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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-554

Medical Review(s)

CLINICAL REVIEW FOR NEW DRUG APPLICATION # 21-554

Drug: Cipro XR® tablet
(ciprofloxacin HCl and ciprofloxacin extended release)

Applicant's Proposed Indications:

- Complicated urinary tract infection, in men and women, caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, [
]*, and *Pseudomonas aeruginosa*^{a*}
- Acute uncomplicated pyelonephritis, in men and women, caused by *Escherichia coli*

*On July 29, 2003 the applicant withdrew their proposal to include [] in the indication for complicated urinary tract infection and added a qualifying statement that *P. aeruginosa* was studied in < 10 patients (see below).

^a Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

General Information:

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Submission/Review Dates:

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Drug Identification:

Generic Name: ciprofloxacin HCl and ciprofloxacin extended release
Pharmacologic Category: fluoroquinolone antibiotic
Proposed Trade Name: Cipro XR®
Molecular Formula: C₁₇H₁₈FN₃O₃ • 3.5 H₂O (ciprofloxacin betaine)
Molecular Weight: 394.3 daltons
Dosage Form: 1000 mg Extended-Release Tablets
Route of Administration: Oral

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ALT	alanine transaminase
AUC	area under the plasma concentration time curve
AUP	acute uncomplicated pyelonephritis
BID	<i>bis in die</i> (twice a day)
C _{max}	maximum plasma concentration
CFU	colony forming units
COSTART	coding symbols for a Thesaurus of adverse reaction terms
cUTI	complicated urinary tract infection
uUTI	uncomplicated urinary tract infection
GGT	gamma glutamyl transpeptidase
MR	modified release
QD	<i>quaque die</i> (once daily)
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TOC	test-of-cure
ULN	upper limit of normal
XR	extended release

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendations on Approvability

In this submission, the applicant demonstrates the activity of 7 to 14 days of treatment with 1000 mg of ciprofloxacin extended release tablets (Cipro XR) in the treatment of patients with complicated urinary tract infection (cUTI) and acute pyelonephritis (AUP). The efficacy of Cipro XR is compared to a FDA-approved regimen consisting of immediate-release ciprofloxacin 500 mg tablets twice daily (Cipro BID) for 7 to 14 days. The Cipro BID regimen is an acceptable comparator since it is approved for severe complicated urinary tract infections at a dose of 250 to 500 mg twice daily for 7 to 14 days.

The study enrolled 1,042 patients (521 patients in both the Cipro XR and Cipro BID groups) and the primary endpoint is bacteriologic eradication, of the baseline organism(s) with no new infection or superinfection, at 5 to 11 days post-therapy.

In the applicant's analysis, bacteriologic eradication in cUTI and AUP patients combined in the valid for efficacy (i.e., Per Protocol) population is 88.8% (183/206) in the Cipro XR group and 85.2% (85.2%) in the Cipro BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (-2.4%, 10.3%) lies above -10%, indicating the non-inferiority of Cipro XR 1000 mg QD compared to Cipro 500 mg BID.

During the review, the Division determined that it was not appropriate to pool results for AUP and cUTI patients due to a significant treatment-by-infection interaction. Therefore, bacteriologic eradication rates for AUP and cUTI were calculated separately by the FDA statistical reviewer. In addition, the Division defined a Modified-to-Treat (MITT) population that includes all patients with a causative organism(s) isolated at baseline and who received at least one dose of study medication. The Division considers analyses of the MITT and PP populations to be co-primary in non-inferiority trials, which is the design of this trial. The MITT population was of particular interest in this trial due to a discrepancy in the number of patients excluded from the PP population between the two treatment arms.

In the MITT population, the bacteriologic eradication rates in AUP patients are 66.2% for Cipro XR compared to 76.3% for Cipro BID [97.5% CI (-26.8, 6.5)]*. In cUTI patients, 59.0% of the Cipro XR group was eradicated compared to 62.9% of the Cipro BID group [97.5% CI (-13.5, 5.7)]*.

In the Per Protocol (PP) population, the bacteriologic eradication rates in AUP patients are 87.5% for Cipro XR compared to 98.1% for Cipro BID [97.5% CI (-34.8, 6.2)]*. In cUTI patients, 89.2% of the Cipro XR group was eradicated compared to 81.4% of the Cipro BID group [97.5% CI (-0.7, 16.3)]*.

* The calculation of the difference in eradication rates between treatment groups [i.e., (Cipro XR minus Cipro BID)] for each stratum alone (i.e., AUP and cUTI) is adjusted for multiple comparisons.

For AUP patients, the 97.5% confidence interval for the treatment difference in bacteriologic eradication rates is below -10% in both the MITT and PP populations, indicating the conditions for non-inferiority of Cipro XR compared to Cipro BID were not met. For cUTI patients, the 97.5% confidence interval of difference is above -10% in the MITT and PP populations (and almost above zero in the PP population), indicating non-inferiority of Cipro XR compared to Cipro BID (and a trend toward superiority in one analysis).

Analyses performed to assess how Cipro XR compared to Cipro BID, with respect to eradication of the baseline pathogen demonstrated comparable eradication rates and clinical response rates.

The applicant demonstrated efficacy of Cipro XR in the PP population of cUTI patients against the following organisms most commonly isolated in urine (≥ 10 in either treatment group): *Escherichia coli* (91/94, 96.8%), *Klebsiella pneumoniae* (20/21, 95.2%), *Enterococcus faecalis* (17/17, 100%), and *Proteus mirabilis* (11/12, 91.6%). For AUP the most common organism was *E. coli* (35/36, 97.2%).

The applicant provided data on less than 10 isolates of *P. aeruginosa* (3/3, 100%), but submitted additional data, including a combination of microbiological data (i.e., MICs) for susceptible isolates of *P. aeruginosa*, along with drug concentration data in plasma and urine, which supports the Division's recommendation of Cipro XR as an appropriate drug to select for the treatment of cUTI caused by susceptible strains of *P. aeruginosa*. The applicant will be asked to continue to gather efficacy and bacteriologic susceptibility information on isolates of *Pseudomonas aeruginosa* in cUTI patients.

The applicant's proposal to reduce the dosage of Cipro XR 1000 mg in patients with severe renal impairment to Cipro XR 500 mg is acceptable. The issue of dosage adjustment of Cipro XR 1000 mg in cUTI and AUP patients with mild to moderate renal impairment has not been addressed by the applicant in this NDA. Upon review of the safety data in the study, the adverse events observed following administration of CIPRO XR 1000 mg to patients with normal renal function and to patients with mild to moderate renal impairment are similar. As a Phase IV commitment, the applicant will be asked to perform Monte-Carlo simulations to characterize drug exposure in patients with mild and moderate renal impairment.

There are no clinically meaningful differences between the Cipro XR and Cipro BID groups in the incidence of any adverse event in the pivotal trial. Of note, however, is the difference in discontinuations due to adverse reactions in the Cipro XR group (5.4%, 28/517) compared to Cipro BID (3.7%, 19/518). The most common reasons for discontinuation, regardless of attributability to study drug, in the Cipro XR group are dizziness and nausea/vomiting [both 25% (5/28)] and headache [11% (3/28)]. In the Cipro BID group the most common reasons for discontinuation are nausea/vomiting and LFT abnormalities [both 21% (4/19)] and diarrhea [11% (2/19)]. No patient discontinued due to dizziness in the Cipro BID group.

In summary, Cipro XR is safe and effective for the treatment of patients with cUTI in patients with susceptible organisms, including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*^a, and *Proteus mirabilis*. In addition, Cipro XR is safe and effective for the treatment of patients with AUP in patients with susceptible organisms, including *Escherichia coli*. The recommendation is for approval of Cipro XR 1000 mg once daily for 7 to 14 days for cUTI and AUP.

^a Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

B. Recommendations on Phase IV Studies and/or Risk Management Steps

- The applicant will be asked to continue to gather efficacy and bacteriologic susceptibility information on isolates of *Pseudomonas aeruginosa* in cUTI patients.
- The applicant will be asked to perform Monte-Carlo simulations to simulate exposure of Cipro XR 1000 mg administered once daily for 14 days to patients with mild and moderate renal impairment (see Clinical Pharmacology and Biopharmaceutics review by Dakshina Chilukuri, Ph.D.).

II. Summary of Clinical Findings

The design for the pivotal study was guided by the following two FDA documents:

- Points to Consider: Urinary Tract Infections. 1997
- Draft Guidance for Industry: Complicated Urinary Tract Infections and Pyelonephritis - Developing Antimicrobial Drugs for Treatment. July 1998.

The applicant also gave consideration to the other following documents when designing this study: the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines (1993), the Committee on Proprietary Medicinal Products' (CPMP) Note for Guidance on Evaluation of New Antibacterial Medicinal Products (1998), and the Infectious Disease Society of America (IDSA) Practice Guidelines Committee publication (1999).

A. Brief Overview of Clinical Program

The primary source of data in support of this application is a prospective, active-controlled, randomized, double blind, multicenter Phase III trial (Study 100275). In this study, a regimen of ciprofloxacin XR 1000 mg once daily tablets administered for 7 to 14 days was compared with the approved (labeled) dosage regimen for conventional (immediate-release) ciprofloxacin tablets (500 mg BID for 7 to 14 days). The protocol inclusion and exclusion criteria for cUTI and AUP are consistent with FDA's 1998 draft guidance document, and included men or non-pregnant women, 18 years of age or older, who presented with clinical signs and symptoms of a cUTI or AUP.

This study was conducted in the United States (US) and Canada at 100 investigative sites. One thousand and forty-two (1,042) adult men and women

with cUTI or AUP were randomized (521 to the Cipro XR group and 521 to the Cipro BID group).

B. Efficacy

Cipro XR was evaluated for the treatment of complicated urinary tract infections (cUTI) and acute uncomplicated pyelonephritis (AUP) in a randomized, double-blind, controlled clinical trial conducted in the US and Canada. The study enrolled 1,042 patients and compared Cipro XR (1000 mg once daily for 7 to 14 days) with immediate-release ciprofloxacin (500 mg twice daily for 7 to 14 days). The primary endpoint for this trial is bacteriologic eradication, of the baseline organism(s) with no new infection or superinfection, at 5 to 11 days post-therapy.

In the applicant's analysis, bacteriologic eradication in AUP and cUTI patients combined in the valid for efficacy (Per Protocol) population is 88.8% (183/206) in the Cipro XR group and 85.2% (85.2%) in the Cipro BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (-2.4%, 10.3%) lies above -10%, indicating the non-inferiority of Cipro XR 1000 mg QD compared to Cipro 500 mg BID.

There are two problems with the applicant's analysis of bacteriologic eradication in cUTI and AUP patients combined in the Per Protocol (PP) population.

- There is a difference in the treatment effect between patients with AUP and cUTI. The eradication rates for the AUP patients are higher in the Cipro BID group (98.1%) than in the Cipro XR group (87.5%). In contrast the eradication rates for cUTI patients are higher in the Cipro XR group (89.2%) than in the ciprofloxacin BID group (81.4%). The applicant pre-specified in the protocol that a Breslow-Day test for treatment-by-infection interaction would be performed prior to combining data from AUP and cUTI patients. The *P* value for the Breslow-Day test is significant at 0.008, indicating that the treatment effect is different between AUP patients and cUTI patients. Therefore, the Division does not consider it appropriate to pool efficacy results for cUTI and AUP patients due to the significant treatment-by-infection interaction.
- The Division defined a Modified-to-Treat (MITT) population that includes all patients with a causative organism(s) isolated at baseline and who received at least one dose of study medication. Although not specified in the protocol by the applicant, the Division considers analyses of the MITT and PP populations to be co-primary in non-inferiority trials, which is the design of this trial. When the MITT population is examined along with reasons for exclusion from the PP population, there are significantly more patients in the Cipro XR group (40%, 136/342) than in the Cipro BID group (29%, 95/324) that had been excluded from the PP population. Exclusions from the PP population are primarily a result of premature discontinuations, which are primarily due to adverse events (2.9% versus 1.7%, respectively) and no valid test-of-cure (TOC) urine culture or lost to follow-up (7.7% versus 4.6%, respectively). A differential rate in exclusion may bias the results of any analysis using this population.

Therefore, the bacteriologic eradication rates for AUP and cUTI were calculated separately by the FDA statistical reviewer and reported for both the MITT and PP populations. Since in the applicant's analysis random assignment of treatment was stratified by infection type, the calculation of the difference in eradication rates between treatment groups for each stratum alone must be adjusted for multiple comparisons (i.e., 97.5% confidence intervals). The bacteriologic eradication rates and their corresponding 97.5% confidence intervals for the differences between rates (Cipro XR minus Cipro BID) for AUP and cUTI patients, at the TOC visit are given in the following table for both the MITT and PP populations.

**Bacteriologic Eradication at TOC (+5 to +11 Days)
in AUP and cUTI Patients**

	MITT*		PP**	
	n/N (% of Patients)	[95% CI of the Difference]	n/N (% of Patients)	[95% CI of the Difference]
AUP Patients				
Cipro XR	47/71 (66.2%)	[-26.8, 6.5]	35/40 (87.5%)	[-34.8, 6.2]
Cipro BID	58/76 (76.3%)		51/52 (98.1%)	
cUTI Patients				
Cipro XR	160/271 (59.0%)	[-13.5, 5.7]	148/166 (89.2%)	[-0.7, 16.3]
Cipro BID	156/248 (62.9%)		144/177 (81.4%)	

* Patients excluded from the Modified Intent-to-Treat group are those with no causative organism at baseline and those who did not receive study drug.

** Patients excluded from the Per Protocol group are those with no causative organism(s) at baseline, no valid TOC urine culture, inclusion/exclusion criteria violation, organism resistant to study drug, protocol violation, non-compliance with dosage regimen, did not receive study drug, inadequate duration of treatment, post-therapy antibiotics, and concomitant antimicrobial therapy.

For AUP patients, the 97.5% confidence interval for the treatment difference in bacteriologic eradication rates is below -10% in both the MITT and PP populations, indicating the conditions for non-inferiority of Cipro XR compared to Cipro BID were not met. For cUTI patients, the 97.5% confidence interval of difference is above -10% in the MITT and PP populations (and almost above zero in the PP population), indicating non-inferiority of Cipro XR compared to Cipro BID (and a trend toward superiority in one analysis).

Additional analyses were performed in an attempt to assess how Cipro XR compared to Cipro BID with respect to persistence of the baseline pathogen and subsequent clinical response.

The applicant's definition of the bacteriologic eradication endpoint used in this protocol considers patients with new infections and superinfections to be treatment failures. In the PP population, of the 40 patients with AUP treated with Cipro XR, 35 were eradicated, 2 had persistence (1 *E. coli* and 1 *E. faecalis*), and 3 developed new infections with *E. faecalis* (2 with *E. coli* as baseline pathogen and one with *S. saprophyticus*). Of the 52 patients with AUP treated with Cipro BID, 51 were eradicated. One patient had persistence of *E. faecalis*.

The most common organism isolated from the urine of AUP patients is *E. coli*. The bacteriologic eradication rate for *E. coli* in the PP population is 97.2% (35/36) for the Cipro XR group and 100% (41/41) in the Cipro BID group.

In the PP population, of the 166 patients with cUTI treated with Cipro XR, 148 were eradicated, 8 had persistence, 5 patients developed superinfections, and 5 patients developed new infections. Of the 177 patients with cUTI treated with Cipro BID, 144 were eradicated, 16 had persistence, 3 patients developed superinfections, and 14 fourteen developed new infections.

The most common organisms isolated from the urine of cUTI patients are *E. coli*, *K. pneumoniae*, *E. faecalis*, and *P. mirabilis*. The bacteriologic eradication rates of these organisms in the PP population, in order, are 96.8% (91/94), 95.2% (20/21), 100% (17/17), and 91.6% (11/12) for the Cipro XR group. In the PP population of the Cipro BID group, the rates, in order, are 97.8% (90/92), 82.6% (19/23), 66.7% (14/21), and 100% (10/10).

Results for all the applicant's secondary variables (i.e., bacteriological response at the late follow-up visit and clinical response at the test-of-cure and late follow-up visits), in the PP population for AUP and cUTI patients separately, are summarized as follows:

- The bacteriologic eradication rates at the late follow-up visit in AUP patients are lower in the Cipro XR group (62.5%, 25/40) compared to the Cipro BID group (67.3%, 35/52). In cUTI patients, the rates are higher in the Cipro XR group (59.6%, 99/166) compared to the Cipro BID group (45.2%, 80/177). The differences between the two patient groups follows a similar trend to the results at the TOC visit.
- The clinical response at the TOC visit in AUP patients is similar for the Cipro XR and Cipro BID groups [97.5% (39/40) and 96.2% (50/52), respectively]. In cUTI patients, the response rates are slightly higher in the Cipro XR group (95.8%, 159/166) compared to the Cipro BID group (91.0%, 161/177).
- The clinical response at the late follow-up visit in AUP patients is slightly lower for the Cipro XR group (75%, 30/40) compared to Cipro BID group (80.8%, 42/52). In cUTI patients, the response rates are slightly higher in the Cipro XR group (72.3%, 120/166) compared to the Cipro BID group (61.6%, 109/177).

Differences seen, if any, in bacteriologic eradication rates between younger and older patients, males and females, and those of various races are not considered clinically meaningful and no adjustments to the dosing of Cipro XR are warranted based on age, sex, or race.

C. Safety

Of the 1042 patients enrolled in the study, 1035 received at least one dose of study drug and are valid for the analysis of safety (517 in the Cipro XR group and 518 in the Cipro BID group). The proportion of patients who experienced at least one adverse event (31.9%) is the same in both treatment groups.

More patients in the Cipro XR group (28 patients or 5.4%) than in the Cipro BID group (19 patients or 3.7%) discontinued study drug due to an adverse event. The most common reasons for discontinuation, regardless of attributability to study drug, in the Cipro XR group are dizziness and nausea/vomiting [both 25% (5/28)] and headache [11% (3/28)]. In the Cipro BID group the most common reasons for discontinuation are nausea/vomiting and LFT abnormalities [both 21% (4/19)] and diarrhea [11% (2/19)]. No patient discontinued due to dizziness in the Cipro BID group.

The most common adverse events in both treatment groups are those occurring in the digestive system [14% (71/517) for Cipro XR and 13% (67/518) for Cipro BID]. The incidence of adverse events for each body system is similar between treatment groups, except for the nervous system. Six percent (6%) of patients in the Cipro XR group (30/517) experienced at least one adverse event involving the nervous system compared with 4% (20/518) in the of Cipro BID group. The events primarily responsible for this difference are dizziness (16 patients [3%] in the Cipro XR group versus 10 patients [2%] in the Cipro BID group), and abnormal dreams, depression, hallucinations, stupor, thinking abnormal, tremor, and hypesthesia (1 patient for each [$<1\%$] versus 0 patients [0%], respectively).

Most patients in both treatment groups who experienced adverse events had events that were assessed by the investigator as mild or moderate in intensity. Adverse events that occurred in at least 2% of patients treated with Cipro XR include nausea (5%), headache (3%), diarrhea (3%), vomiting (3%), dizziness (3%), dyspepsia (2%), and vaginal moniliasis (2%). Cipro BID has a similar profile of adverse events occurring in at least 2% of patients, with a slightly higher incidence of headache (5%).

Study drug-related (possible or probable relationship) adverse events were reported in 13% (68/517) of patients in the Cipro XR group and 14% (70/518) of patients in the Cipro BID group. Those occurring in 2% or more of patients in either treatment group include headache, nausea, diarrhea, dizziness, and vaginal moniliasis.

A small proportion of patients had events that were assessed by the investigator as severe in intensity. Seven percent (35/517) of all valid for safety patients in the Cipro XR group and 5% (28/518) in the Cipro BID group experienced at least one adverse event assessed by the investigator as severe in intensity. The number of severe adverse events represents 14.6% (50/342) and 12.8% (39/304), respectively, of the total number of adverse events reported.

Four patient deaths were reported during the study (3 in the Cipro XR group and one in the Cipro BID group). All four patients were in the older age range (76 to 95 years), had a diagnosis of cUTI with one underlying condition, and had other

concurrent medical conditions requiring concomitant medications. In all cases, the adverse event resulting in death was judged by the investigator to be of unlikely or no relationship to study drug. This Reviewer concurs with the investigator's opinion in all cases.

Patients experiencing non-fatal serious adverse events (SAEs) is 5% in both treatment groups, (28/517 and 24/518, respectively). All SAEs reported in the Cipro XR group were judged by the investigators to be unlikely or not related to study drug.

In the two treatment groups, the incidence of clinically significant ($>1.8 \times \text{ULN}$) abnormalities in SGOT and SGPT is the same (2%). For abnormalities in SGOT and SGPT that are $>3 \times \text{ULN}$, the incidence is 1% in the Cipro XR group and 2% in the Cipro BID group. Two patients ($<1\%$) in the Cipro XR group had liver function test abnormalities that were reported as adverse events. In both cases, the events resolved and did not require discontinuation of study drug. Seven patients (1%) treated with Cipro BID had abnormal liver function test results that were reported as adverse events. In 4 of these 7 patients, the liver function test abnormalities were a reason for discontinuation of study medication. Only one of the 4 patients in the Cipro BID group who discontinued prematurely for liver function test abnormalities had all tests within the normal range at baseline.

The incidence of other laboratory test abnormalities is low and comparable between the two treatment groups. Descriptive statistics of the change from baseline in laboratory test results does not reveal any trends that appear to be uniquely associated with Cipro XR treatment.

Overall, there are no clinically meaningful differences in the safety profile of either treatment on the basis of age, sex, or race.

D. Dosing, Regimen, and Administration

The dosage regimen of Cipro XR 1000 mg administered daily for 7 to 14 days for the treatment of cUTI and AUP is based on Phase I studies of this formulation and the approved labeling for conventional ciprofloxacin tablets. The current recommended dosage for ciprofloxacin tablets in the treatment of mild/moderate to severe/complicated urinary tract infections is 250 to 500 mg BID for 7 to 14 days. The Phase I studies for Cipro XR (Studies 10324 and 10339) indicate that the ciprofloxacin AUC attained following the oral administration of Cipro XR 1000 mg tablets every 24 hours is similar to the values attained following the oral administration of conventional ciprofloxacin 500 mg tablets every 12 hours (16.5 mg*h/L versus 16.0 mg*h/L, respectively, in Study 10324; and 15.4 mg*h/L versus 14.8 mg*h/L, respectively, in Study 10339). The C_{max} of Cipro XR 1000 mg given every 24 hours is about 46% higher than the C_{max} for Cipro 500 mg tablets given every 12 hours.

E. Special Populations

Pediatric patients (< 18 years) and patients with significant renal impairment (serum creatinine >3.0 mg/dL or creatinine clearance <30 mL/min*1.73 m²) or hepatic impairment (baseline SGOT or SGPT and/or total bilirubin greater than 3 times the upper limit of normal), and pregnant women were excluded from the Cipro XR development program. Therefore it is not possible to comment on the efficacy or adverse event profile in these populations.

1. Efficacy

Age

In the Reviewer's opinion, differences, if any, seen in the bacteriologic eradication rates between the following patient groups are not considered clinically meaningful: young (< 65 years) and old (≥ 65 years); male and female; Caucasians, Blacks, and Hispanics. No adjustments to the dosing of Cipro XR are warranted based on age, sex or race.

2. Safety

Age

In the Reviewer's opinion, differences, if any, seen in adverse events reported for the following patient groups are not considered clinically meaningful: young (< 65 years) and old (≥ 65 years); male and female; Caucasians, Blacks, and Hispanics. Reporting of adverse events by age, sex, or race are not warranted in the labeling of Cipro XR.

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CLINICAL REVIEW

I. Introduction and Background

A new extended-release formulation of ciprofloxacin tablets (Cipro XR) has been developed in 500 mg and 1000 mg (ciprofloxacin equivalent) strengths and is intended to be dosed once daily. The Cipro XR 500 mg tablet was approved for the treatment of patients with uncomplicated urinary tract infections (uUTI) on December 13, 2002. The Cipro XR 1000 mg tablet is intended for the treatment of patients with complicated UTI (cUTI), including acute uncomplicated pyelonephritis (AUP) and is the subject of this NDA submission.

Prior to the approval of Cipro XR for uUTI, there were two other marketed oral formulations of ciprofloxacin: Cipro® tablets (ciprofloxacin hydrochloride) and Cipro® oral suspension (ciprofloxacin). Both formulations are approved for the treatment of the following infections caused by susceptible strains of specifically identified microorganisms: acute sinusitis, lower respiratory tract infections, urinary tract infections, chronic bacterial prostatitis, skin and skin structure infections, bone and joint infections, infectious diarrhea that warrants antibacterial therapy, typhoid fever, nosocomial pneumonia, acute uncomplicated cystitis in females, empiric therapy of febrile neutropenic patients, complicated intraabdominal infections, uncomplicated cervical and urethral gonorrhea, and post-exposure inhalation anthrax. The maximum oral daily dose of Cipro® tablets and oral suspension approved for use in humans is 750 mg twice daily.

Cipro XR is formulated to release drug at a slower rate compared to the conventional immediate release tablets. Approximately 35% of the dose XR dose of ciprofloxacin is contained within an immediate release component, while the remaining 65% is contained in a slow release matrix. Cipro XR is designed to release the entire dose prior to the tablet reaching the distal region of the small intestine.

The Cipro XR formulation exhibits dissolution characteristics aimed to deliver the equivalent exposure to drug, in terms of area under the curve (AUC) as the corresponding approved conventional ciprofloxacin tablet BID treatment. In other words, one Cipro XR 1000 mg tablet has a similar AUC compared with two 500 mg conventional ciprofloxacin tablets given at once. Although the AUC of the two formulations is similar, the peak concentration (C_{max}) achieved with Cipro XR is lower compared to an equivalent dose of the conventional tablet. In other words, one Cipro XR 1000 mg tablet has a lower C_{max} than two 500 mg conventional ciprofloxacin tablets given at once.

A. Established and Proposed Trade Name of Drug, Drug Class, Applicant's Proposed Indications, Dose, Regimens, Age Groups

Drug

Generic Name: ciprofloxacin HCl and ciprofloxacin extended release
Pharmacologic Category: fluoroquinolone antibiotic
Proposed Trade Name: Cipro XR®
Molecular Formula: C₁₇H₁₈FN₃O₃ • 3.5 H₂O (ciprofloxacin betaine)
Molecular Weight: 394.3 daltons
Dosage Form: 1000 mg Extended-Release Tablets
Route of Administration: Oral

Applicant's Proposed Indications:

- Complicated urinary tract infection, in men and women, caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, *Citrobacter diversus*, *Morganella morganii*, and *Pseudomonas aeruginosa*^{a*}
- Acute uncomplicated pyelonephritis, in men and women, caused by *Escherichia coli*

^aOn July 29, 2003 the applicant withdrew their proposal to include *Citrobacter diversus* in the indication for complicated urinary tract infection and added a qualifying statement that *P. aeruginosa* was studied in < 10 patients (see below).

^{*} Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

Applicant's Proposed Dosing and Administration

Indication	Unit Dose	Usual Duration
Complicated Urinary Tract Infection	1000 mg	7-14 Days
Acute Uncomplicated Pyelonephritis	1000 mg	7-14 Days

B. State of Armamentarium for Indications

1. Other FDA-approved Quinolones

Ciprofloxacin (Cipro®): Urinary Tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis*.

Ofloxacin (Floxin®): Complicated UTI due to *Citrobacter diversus**, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, or *Pseudomonas aeruginosa** (*denotes efficacy in less than 10 cases).

Levofloxacin (Levaquin®): Complicated UTI (mild to moderate) due to *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, or *Enterococcus faecalis*. Acute pyelonephritis (mild to moderate) caused by *Escherichia coli*.

Lomefloxacin (Maxaquin®): Complicated UTI due to *Citrobacter diversus**, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, or *Enterobacter cloacae** (*denotes efficacy in less than 10 cases).

NOTE: In clinical trials in patients experiencing CUTIs due to *Pseudomonas aeruginosa*, 12 of 16 patients had the microorganism eradicated from the urine after therapy with lomefloxacin. None of the patients had concomitant bacteremia. Serum levels of lomefloxacin do not reliably exceed the MIC of *Pseudomonas* isolates. THE SAFETY AND EFFICACY OF LOMEFLOXACIN IN TREATING PATIENTS WITH PSEUDOMONAS BACTEREMIA HAVE NOT BEEN ESTABLISHED.

Enoxacin (Penetrex®): Complicated UTI due to *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa*. (*Efficacy for this organism was studied in fewer than 10 infections.)

Gatifloxacin (Tequin®): Complicated UTI due to *Escherichia coli*, *Proteus mirabilis*, or *Klebsiella pneumoniae*. Pyelonephritis caused by *Escherichia coli*.

2. Quinolone that did not receive approval for the cUTI and AUP Indication

Trovaflaxacin (Trovan®): Based on a randomized, comparative, double-blind trial of trovaflaxacin and ciprofloxacin in the treatment of complicated urinary tract infections and a supportive non-comparative study, the MO did not recommend approval for the requested indication of complicated UTI caused by *Escherichia coli* and *Klebsiella pneumoniae*. This decision was based on the inability of the applicant to show equivalence with an approved comparator. Additionally, the MO found that the overall bacteriologic efficacy rate at the EOT (cumulative: 152/196 (77.5%)) was lower than that of other approved quinolone antimicrobials. Cumulative pathogen eradication rates for the requested pathogens, *Escherichia coli* and *Klebsiella pneumoniae* were also lower.

3. Other FDA-approved Antibacterials (other than quinolones)

Trimethoprim/Sulfamethoxazole (Bactrim®): for the treatment of UTIs due to susceptible strains of the following organisms: *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Morganella morganii*, and *Proteus vulgaris*.

Sulfisoxazole (Gantrisin®): Acute, recurrent, or chronic UTIs (primarily pyelonephritis, pyelitis, and cystitis,) due to susceptible organisms (usually *Escherichia coli*, *Klebsiella*- *Enterobacter*, *Staphylococcus*, *Proteus mirabilis* and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies.

Loracarbef (Lorabid®): Uncomplicated pyelonephritis caused by *Escherichia coli*.

Cefepime (Maxipime®): Uncomplicated and Complicated UTIs (including pyelonephritis) caused by *Escherichia coli* or *Klebsiella pneumoniae* when the infection is severe, or caused by *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*, when the infection is mild to moderate, including cases associated with concurrent bacteremia associated with these microorganisms.

4. Efficacy of Conventional Ciprofloxacin versus Comparators for cUTI and AUP

Ciprofloxacin has been marketed worldwide since 1988 and is approved to treat mild/moderate to severe/complicated UTI. The recommended dosage regimen for conventional ciprofloxacin tablets or oral suspension is 250 to 500 mg BID for 7 to 14 days.

The efficacy of ciprofloxacin in treating cUTI and AUP infections compared to other antimicrobials can be seen in Tables 1 and 2, respectively.

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TABLE 1
Prospective, Randomized, Double Blind, Controlled Clinical Studies Evaluating Treatment of Conventional Ciprofloxacin In Complicated Urinary Tract Infections

Treatment (dose and duration)	Bacteriologic Cure ^a (end of treatment)	Clinical Cure ^a (end of treatment)	Follow-up Efficacy	Reference
Ciprofloxacin 250 mg BID x 7 days	136/151 (90%) ^{b,c}	140/144 (77%) ^b	111/114 (77%) ^{d,e}	1
Ofloxacin 200 mg BID x 7 days	130/149 (87%)	108/142 (76%)	108/142 (76%)	
Ciprofloxacin 500 mg BID x 10-14 days	194/240 (81%) ^f	198/231 (86%) ^f	186/219 (84%) ^g	2
Sparfloxacin 200 mg x 1 day followed by 100 mg once daily x 9 to 13 days	168/233 (72%)	193/221 (87%)	181/215 (84%)	
Ciprofloxacin 500 mg BID x 10 days	93% ^{b,i}	100/113 (89%) ^b	Relapse: 10	3
Levofloxacin 250 mg QD x 10 days	91%	116/126 (92%)	Relapse: 13	
Ciprofloxacin 500 mg BID x 7-10 days	62/83 (83%) ^{b,h}	70/75 (93%) ^b	52/70 (74%) ^f	4
Gatifloxacin 400 mg QD x 7-10 days	61/66 (92%)	61/66 (92%)	51/61 (84%)	

^a Evaluable patients

^b 5 to 9 days post-treatment

^c Urine culture sterile

^d 28 to 42 days post-treatment

^e Urine culture sterile and clinical cure symptom-free at follow-up visits

^f 4 to 14 days post-treatment

^g Continued clinical cure at 15 to 56 days post-treatment

^h Eradication

ⁱ 4 to 6 weeks post-treatment

^j Clinical cure at 29 to 42 days post-treatment

References for Table 1

1. Raz R, Naber KG, Raizenberg C, et al. Ciprofloxacin 250 mg twice daily versus ofloxacin 200 mg twice daily in the treatment of complicated urinary tract infections in women. *Eur J Clin Micro Infect Dis* 2000;19:327-31.
2. Naber KG, di Silverio F, Geddes A, et al. Comparative efficacy of sparfloxacin versus ciprofloxacin in the treatment of complicated urinary tract infection. *J Antimicrob Chemother* 1996 May;37 Suppl A:135-44.
3. Richard GA, Childs SJ, Fowler CL, et al. Safety and efficacy of levofloxacin versus ciprofloxacin in complicated tract infections in adults. *Pharmacy and Therapeutics* 1998 (October);23:534-42.
4. Cox CE, Marbury TC, Pittman WG, et al. A randomized, double-blind, multi-center comparison of gatifloxacin versus ciprofloxacin in the treatment of complicated urinary tract infections and pyelonephritis. *Clin Therapeutics* 2002;24:223-36.

TABLE 2
Prospective, Randomized, Double Blind, Controlled Clinical Studies Evaluating Treatment of Conventional Ciprofloxacin In Acute Uncomplicated Pyelonephritis

Treatment (dose and duration)	Bacteriologic Cure ^a (end of treatment)	Clinical Cure ^a (end of treatment)	Follow-up efficacy	Reference
Ciprofloxacin 500 mg BID x 7 days ± initial 400 mg IV dose	112/113 (99%) ^{b,d}	109/113 (96%) ^{b,c}	96/106 (91%) ^{e,i}	1
Trimethoprim/Sulfamethoxazole 160/800 mg BID x 14 days ± initial 1 gram IV ceftriaxone	90/101 (89%)	92/111 (83%)	82/106 (77%)	
Ciprofloxacin 500 mg BID	94% ^{g,i}	51/58 (88%) ^g	≤6.5% ^h	2
Levofloxacin 250 mg QD	95%	82/89 (92%)	13%	
Lomefloxacin 400 mg QD	94%	31/39 (80%)	≤6.5%	
Ciprofloxacin 500 mg BID x 7-10 days	17/20 (85%) ^{g,i} <i>E. coli</i> 100%	19/20 (95%) ^g	18/19 (95%) ⁱ	3
Gatifloxacin 400 mg QD x 7-10 days	23/25 (92%) <i>E. coli</i> 95%	25/25 (100%)	22/25 (88%)	

^a Evaluable patients

^b 4 to 11 days post-treatment

^c 95% CI, 0.06 - 0.22 for the difference, P=0.002

^d 95% CI, 0.04 - 0.16 for the difference, P=0.004

^e Continued clinical cure 22 to 48 days post-treatment

^f 95% CI, 0.03 - 0.23 for the difference, P=0.02

^g 5 to 9 post days treatment

^h Microbiologic relapse rate at 4 to 6 weeks

ⁱ Clinical cure at 29 to 42 days post-treatment

References for Table 2

1. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial. *JAMA* 2000;283(12):1583-90.
2. Richard GA, Klimberg IN, Fowler CL, et al. Levofloxacin versus ciprofloxacin versus lomefloxacin in acute pyelonephritis. *Urology* 1998;52:51-5.
3. Cox CE, Marbury TC, Pittman WG, et al. A randomized, double-blind, multi-center comparison of gatifloxacin versus ciprofloxacin in the treatment of complicated urinary tract infections and pyelonephritis. *Clin Therapeutics* 2002;24:223-36.

C. Important Milestones in Product Development

The regulatory history of Cipro XR 1000 mg tablets for the treatment of cUTI and AUP is outlined in the following sequence of events:

On November 29, 2000, Bayer submitted the IND (61,331) for Cipro® XR* (Ciprofloxacin) extended-release tablets.

On February 13, 2001, a pre-IND/End of Phase II meeting was held with the FDA. The FDA agreed one trial in patients with complicated urinary tract infections would be acceptable for registration. The Division recommended a 10% delta. After the meeting, Bayer proposed that separate NDAs be submitted for uncomplicated and complicated urinary tract infection and the FDA agreed.

Cipro XR* for uncomplicated urinary tract infection (NDA 21-473) was submitted on March 4, 2002.

Cipro XR for uncomplicated urinary tract infection (NDA 21-473) was approved on December 13, 2002. The indication reads as follows:

Uncomplicated Urinary Tract Infections (Acute Cystitis) caused by *Escherichia coli*, *Proteus mirabilis*, *Enterococcus faecalis*, or *Staphylococcus saprophyticus*^a.

- ^a Treatment of infections due to this organism in this organ system was studied in fewer than 10 patients.
- * The original trade name proposed by Bayer was . On June 6, 2002 at a meeting with the Division as well as representatives from Office of Drug Safety and DDMAC, the portion of the drug name was discussed. It was suggested by the Agency that another suffix similar to other approved extended release products would be more appropriate. On July 18, 2002, Bayer submitted a letter confirming the change in trade name from Ciprofloxacin to Cipro XR (ciprofloxacin hydrochloride and ciprofloxacin extended release tablets).

D. Other Relevant Information

The United States is the first country in which Bayer has submitted an application for approval of ciprofloxacin XR 1000 mg oral tablets. However, multiple submissions around the world in the months following this submission are planned.

Immediate release ciprofloxacin has been studied previously under multiple IND and NDAs.

Product	Form	IND Reference #	NDA Reference #
Oral Tablet	Ciprofloxacin HCl	21,804	19-537
Intravenous	Ciprofloxacin	25,173	19-847
Intravenous 0.2% in 5% Dextrose	Ciprofloxacin	25,173	19-857
Intravenous 0.2% in 0.9% Saline	Ciprofloxacin	25,173	19-858
Oral Suspension	Ciprofloxacin	43,007	20-780

II. Significant Findings from Chemistry, Pharmacology/Toxicology, Microbiology, Clinical Pharmacology/Biopharmaceutics, and Biostatistics

A. Chemistry

This application can be approved from the chemistry perspective.

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of Cipro XR 1000 mg. During the review a number of issues, including the following were resolved:

- The acceptance criteria, included in the specification for one of the drug substances (i.e., ciprofloxacin base), were revised.
- The specification for the drug product was also revised to include test and acceptance criteria for water content. Acceptance criteria for the impurities in the drug product were revised.

The trade name was found acceptable by OPDRA and by the Division (HFD-590) for this NDA. The established name was further consulted with the Labeling and Nomenclature Committee and they recommended the following:

CIPRO XR (ciprofloxacin* extended-release tablets)

* as ciprofloxacin † and ciprofloxacin hydrochloride

† does not comply with the loss on drying test and residue on ignition test of the USP monograph.

See complete review by Dorota Matecka, Ph.D., Chemistry Reviewer, in HFD-590 (DSPIDP) filed with this NDA (21-554).

B. Pharmacology/Toxicology

This application can be approved from the pharmacology/toxicology perspective.

The applicant did not submit new pharmacology/toxicology data in support of this NDA only a cross-reference statement to the previously approved Cipro IV, Cipro tablets, and Cipro oral suspension NDAs, as agreed upon with the Division.

See review by Steven Hundley, Ph.D., Pharmacology/Toxicology Reviewer, in HFD-590 (DSPIDP) filed with this NDA (21-554).

C. Microbiology

This application can be approved from the microbiological perspective.

See complete review by Peter A. Dionne, M.S., Microbiologist in HFD-590 (DSPIDP) filed with this NDA (21-554).

During the clinical study (100275) the susceptibility of the causative organisms was determined at the central laboratory [] Broth microdilution susceptibility tests were performed according to National

Committee for Clinical Laboratory Standards (NCCLS) guidelines. *Escherichia coli* was the most frequently isolated organism (n=263), followed by *Klebsiella pneumoniae* (n=50), *Enterococcus faecalis* (n=46), and *Proteus mirabilis* (n=26). The MIC₉₀ for *E. coli* was 0.06 µg/mL, while the MIC₉₀ for *K. pneumoniae* and *P. mirabilis* were 0.5 µg/mL and 2 µg/mL, respectively. The MIC₉₀ for the other 46 isolates of Enterobacteriaceae was ≤ 1 µg/mL and the MIC₉₀ for *E. faecalis* was 2 µg/mL.

The by-pathogen eradication rates were consistent in the two treatment groups. Cipro XR had a better eradication rate against *Enterococcus faecalis* than did Cipro BID. Eradication rates for *E. coli*, by far the most common organism, were high for both treatment groups. There were very few isolates of *Enterobacter aerogenes* or *Pseudomonas aeruginosa*. Persistence was not associated with elevated MICs for any of the organisms.

In patients valid for efficacy that had bacteriologic persistence or were clinical failures at the TOC and follow-up visits, there were more bacteriologic persistence and clinical failures seen in the Cipro BID group (n = 26) compared with the Cipro XR group (n = 15).

The development of resistance during therapy was low.

D. Clinical Pharmacology/Biopharmaceutics

See complete review by Dakshina Chilukuri, PhD, Clinical Pharmacology/Biopharmaceutics Reviewer, in HFD-590 (DSPIDP) filed with this NDA (21-554).

A total of five clinical pharmacology studies were conducted with Cipro XR 1000 mg in healthy volunteers. These studies compared pharmacokinetics of the Cipro XR 1000 mg once-daily regimen to the corresponding immediate release regimen (e.g., 1000 mg XR vs. 500 mg immediate release BID) and examined the effects of food on the performance of the XR tablet. In addition, the drug interaction studies to study the effect of Maalox and Omeprazole on the pharmacokinetics of Cipro XR were also conducted. These studies were reviewed in NDA 21-473 as part of the Cipro XR 500 mg tablet formulation.

The 24-hour area under the curve (AUC) obtained following administration of 1000 mg Cipro XR was shown to be equivalent to that attained with BID dosing of 500 mg immediate release ciprofloxacin. The bioavailability of the XR tablet was not altered by administration with food (either a high-fat or a low-fat meal), and did not change upon multiple dosing for 5 days. The C_{max} following administration of the 1000 mg XR tablet was higher than that observed for the 500 mg immediate release tablet. Trough plasma concentrations are lower with the 1000 mg XR once-daily regimen compared to the 500 mg BID regimen. However, urine concentrations of ciprofloxacin following dosing with 1000 mg Cipro XR are maintained well above (>100-fold) the *in vitro* MIC₉₀ for *Escherichia coli* (about 0.03 µg/mL).

The applicant's proposal to reduce the dosage of Cipro XR 1000 mg in patients with severe renal impairment to Cipro XR 500 mg is acceptable. The issue of

dosage adjustment of Cipro XR 1000 mg in cUTI and AUP patients with mild to moderate renal impairment has not been addressed by the applicant in this NDA. Specifically, it is unknown if the C_{max} and AUC following administration of Cipro XR 1000 mg to patients with mild to moderate renal impairment would result in exposure causing higher incidence of adverse events.

Upon review of the safety data in Clinical Study 100275 [see more details in this review], the adverse events observed following administration of CIPRO XR 1000 mg to patients with normal renal function and to patients with mild to moderate renal impairment are similar. However, the exposure following administration of Cipro XR 1000 mg in patients with mild to moderate renal impairment is likely to be higher than the exposure obtained after administration of 750 mg bid of immediate release ciprofloxacin (the highest approved dose). But considering the overall safety profile of Cipro XR in this NDA, it may be acceptable to administer a dose of Cipro XR 1000 mg to patients with mild to moderate renal impairment suffering from cUTI and AUP.

In summary, this application can be approved from the clinical pharmacology and biopharmaceutics perspective. For patients with mild and moderate renal impairment, no dosage adjustments are recommended, at this time. As a Phase IV commitment, the applicant will be asked to perform additional Monte-Carlo simulations to characterize the exposure of Cipro XR 1000 mg (administered once daily for 14 days) in patients with mild and moderate renal impairment. Based on these results, changes in labeling may be recommended at a later time.

E. Biostatistics

The results of the treatment group comparisons of the primary efficacy endpoint (i.e., bacteriologic outcome at TOC) between infection types were not consistent in the clinical study (100275). A treatment-by-infection-type interaction was observed indicating that the treatment effect is different between AUP patients and cUTI patients and as such these two strata should be considered separately.

Within the cUTI stratum, it is the opinion of the statistical reviewer that Cipro XR has been shown to be noninferior to Cipro XR for the bacteriological eradication rate at TOC endpoint in the PP analysis group. Analysis of the mITT group for this endpoint included disproportionately more subjects in the Cipro XR arm who were excluded from the PP analysis group. The majority of these subjects were considered failures in the analysis since their bacteriological response at TOC was likely missing or indeterminate. Within the cUTI stratum in the mITT group, the noninferiority criterion was not met.

Within the AUP stratum, it is the opinion of the statistical reviewer that noninferiority of Cipro XR to Cipro BID for the bacteriological eradication rate at TOC endpoint in the PP analysis group has not been demonstrated. In fact within the AUP stratum, Cipro XR appears to be worse than Cipro BID for the eradication at TOC endpoint in the PP analysis group. A similar trend is observed in the mITT group for this endpoint.

These results for the primary endpoint within each of the strata are not dependent on the use of the expanded 5 to 11 day TOC window rather than the 5 to 9 day window defined in the original protocol.

Secondary endpoints for this study included the bacteriological response at follow-up and clinical responses at TOC and follow-up.

- The eradication rates at follow-up for the cUTI subjects were higher in the Cipro XR group than in the Cipro BID group. Conversely, the eradication rates at the follow-up visit for the AUP subjects were higher in the Cipro BID group than in the Cipro XR group. These trends are consistent with that of the bacteriologic endpoint at the TOC visit suggesting that the treatment effect may be different in the two strata.
- The clinical success rates at TOC for the cUTI subjects in the PP analysis group were slightly higher in the Cipro XR group than in the Cipro BID group. The clinical success rates at the TOC visit for the AUP subjects were similar in the Cipro BID and Cipro XR groups in the PP analysis group. The Cipro XR group had slightly lower clinical success rates than the Cipro BID group in the mITT analysis.
- The success rates at the follow-up visit for the cUTI subjects in the PP analysis group were higher in the Cipro XR group than in the Cipro BID group. Conversely, the clinical success rates at the follow-up visit for the AUP subjects were slightly lower in the Cipro XR group than in the Cipro BID group in the PP analysis group. Similar trends were observed in the mITT analysis. These trends are consistent with the treatment-by-infection-type interaction observed with the bacteriologic endpoint.

It is the opinion of the statistical reviewer that Cipro XR has been shown to be non-inferior to Cipro BID in terms of the bacteriologic endpoint at TOC in cUTI subjects. Noninferiority of Cipro XR in comparison to Cipro BID in terms of the bacteriologic endpoint at TOC within AUP subjects has not been demonstrated.

See complete review by Ruthanna Davi, M.S., Biostatistician in HFD-590 (DSPIDP) filed with this NDA (21-554).

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Ciprofloxacin XR tablets 1000 mg are bi-layer tablets composed of an immediate release layer, a controlled release layer, and a coating.

The outer controlled release layer releases approximately 35% of the dose immediately after intake, and the inner immediate release layer has an immediate onset of release with a marginally slower release rate profile. Both the immediate-release and controlled-release layers of the tablets are composed of different ratios of ciprofloxacin hydrochloride and ciprofloxacin base.

The XR formulation was designed to deliver the equivalent drug exposure (in terms of AUC) as the approved conventional ciprofloxacin daily dose (i.e., 1000 mg Cipro XR is equivalent to two 500 mg conventional ciprofloxacin tablets). Although the two formulations have similar AUCs, the peak concentration (C_{max}) achieved following a 1000 mg dose of the XR formulation is higher than that achieved with the 500 mg dose of the conventional ciprofloxacin tablet.

Through all phases of development the same formulation has been used.

Reviewer's Comment: The following information on the pharmacokinetics of Ciprofloxacin XR 500 mg and 1000 mg is from the applicant's proposed label (May 30, 2003). The data has been verified by the Clinical/Pharmacology Reviewer.

Maximum plasma ciprofloxacin concentrations are attained between 1 and 4 hours after dosing with CIPRO XR. In comparison to the 250 mg and 500 mg ciprofloxacin immediate-release BID treatment, the C_{max} of CIPRO XR 500 mg and 1000 mg once daily are higher than the corresponding BID doses, while the AUCs over 24 hours are equivalent.

The following table compares the pharmacokinetic parameters obtained at steady state for these four treatment regimens (500 mg QD CIPRO XR versus 250 mg BID ciprofloxacin immediate-release tablets and 1000 mg QD CIPRO XR versus 500 mg BID ciprofloxacin immediate-release).

Ciprofloxacin Pharmacokinetics (Mean \pm SD) Following CIPRO® and CIPRO XR Administration

	C_{max} (mg/L)	AUC _{0-24h} (mg•h/L)	T _{1/2} (hr)	T _{max} (hr) [§]
CIPRO XR 500 mg QD	1.59 \pm 0.43	7.97 \pm 1.87	6.6 \pm 1.4	1.5 (1.0 – 2.5)
CIPRO 250 mg BID	1.14 \pm 0.23	8.25 \pm 2.15	4.8 \pm 0.6	1.0 (0.5 – 2.5)
CIPRO XR 1000 mg QD	3.11 \pm 1.08	16.83 \pm 5.65	6.31 \pm 0.72	2.0 (1 – 4)
CIPRO 500 mg BID	2.06 \pm 0.41	17.04 \pm 4.79	5.66 \pm 0.89	2.0 (0.5 – 3.5)

§ median (range)

Results of the pharmacokinetic studies demonstrate that CIPRO XR may be administered with or without food (e.g. high-fat and low-fat meals or under fasted conditions).

Distribution

The volume of distribution calculated for intravenous ciprofloxacin is approximately 2.1 – 2.7 L/kg. Studies with the oral and intravenous forms of ciprofloxacin have demonstrated penetration of ciprofloxacin into a variety of tissues. The binding of ciprofloxacin to serum proteins is 20% to 40%, which is not likely to be high enough to cause significant protein binding interactions with other drugs. Following administration of a single dose of CIPRO XR, ciprofloxacin concentrations in urine collected up to 4 hours after dosing averaged over 300 mg/L for both the 500 mg and 1000 mg tablets; in urine

excreted from 12 to 24 hours after dosing, ciprofloxacin concentration averaged 27 mg/L for the 500 mg tablet, and 58 mg/L for the 1000 mg tablet.

Metabolism

Four metabolites of ciprofloxacin were identified in human urine. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. The primary metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for roughly 3% to 8% of the total dose. Other minor metabolites are desethylene ciprofloxacin (M1), and formylciprofloxacin (M4). The relative proportion of drug and metabolite in serum corresponds to the composition found in urine. Excretion of these metabolites was essentially complete by 24 hours after dosing.

Elimination

The elimination kinetics of ciprofloxacin are similar for the immediate-release and the CIPRO XR tablet. In studies comparing the CIPRO XR and immediate-release ciprofloxacin, approximately 35% of an orally administered dose was excreted in the urine as unchanged drug for both formulations. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with immediate-release ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing with the immediate-release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1% to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20% to 35% of an oral dose of immediate-release ciprofloxacin is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

Special Populations

Pharmacokinetic studies of the immediate-release oral tablet (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (> 65 years) as compared to young adults. C_{max} is increased 16% to 40%, and mean AUC is increased approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant.

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. No dose adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg CIPRO XR. For indications where 1000 mg is the appropriate dose, the dosage of CIPRO XR should be reduced to CIPRO XR 500 mg q 24 h in patients with creatinine clearance below 30 mL/min.

In studies in patients with stable chronic cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of

ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated.

Drug-drug Interactions

Previous studies with immediate-release ciprofloxacin have shown that concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc.

Antacids: When CIPRO XR given as a single 1000 mg dose (twice the recommended daily dose) was administered two hours before, or four hours after a magnesium/aluminum-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in the mean C_{max} of ciprofloxacin. The reduction in the mean AUC was 24% and 26%, respectively. CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin preparations with zinc. Although CIPRO XR may be taken with meals that include milk, concomitant administration with dairy products or with calcium-fortified juices alone should be avoided, since decreased absorption is possible.

Omeprazole: When CIPRO XR was administered as a single 1000 mg dose concomitantly with omeprazole (40 mg once daily for three days) to 18 healthy volunteers, the mean AUC and C_{max} of ciprofloxacin were reduced by 20% and 23%, respectively. The clinical significance of this interaction has not been determined.

B. Pharmacodynamics

The minimum inhibitory concentrations at which 90% of organisms were inhibited (MIC_{90}) for the most common causative pathogens in Study 100275 above are as follows: *E. coli* (0.06 µg/mL); *K. pneumoniae* (0.5 µg/mL); *E. faecalis* (2.0 µg/mL); *P. mirabilis* (2.0 µg/mL); *E. aerogenes* (0.06 µg/mL), and *P. aeruginosa* (0.5 µg/mL). The MIC_{90} for other isolates of Enterobacteriaceae is <1.0 µg/mL. Urinary concentrations of ciprofloxacin towards the end of the dosing interval in subjects administered Cipro XR 1000 mg QD for 5 days, are above these MIC levels for the predominant uropathogens in both cUTI and AUP.

In addition, the clinical efficacy of Cipro XR in treating cUTI is demonstrated for *E. coli*, *K. pneumoniae*, and *E. faecalis* and shown in Table 8. Three infections secondary to *P. aeruginosa* were successfully treated in the Cipro XR group with an eradication rate of 100% (3/3), and an additional patient with AUP secondary to *P. aeruginosa* was also successfully treated with Cipro XR.

TABLE 3
Bacteriological Eradication at TOC Visit (+5 to +11 Days) by Organism
Patients Valid for Efficacy

	n/N (%)	
	Cipro XR	Cipro BID
AUP Patients		
<i>Escherichia coli</i>	35/36 (97%)	41/41 (100%)
cUTI Patients		
<i>Escherichia coli</i>	91/94 (97%)	90/92 (98%)
<i>Klebsiella pneumoniae</i>	20/21 (95%)	19/23 (83%)
<i>Enterococcus faecalis</i>	17/17 (100%)	14/21 (67%)
<i>Proteus mirabilis</i>	11/12 (92%)	10/10 (100%)

IV. Clinical Review Methods

A. Structure of the Review

The primary source of data for this application is a prospective, active-controlled, randomized, double blind, multicenter Phase III trial (Study 100275).

Reviewer's Comment: According to the Draft Guidance for Industry (Complicated Urinary Tract Infections and Pyelonephritis - Developing Antimicrobial Drugs for Treatment. July 1998) a single statistically adequate and well-controlled trial establishing safety and effectiveness to an approved product should be conducted. In addition, a comparative or noncomparative trial should also be conducted.

For this application the applicant conducted a single statistically adequate and well-controlled trial. In lieu of an additional trial the Division (and the applicant) relied on previous data gathered from trials of immediate-release ciprofloxacin (tablets or oral suspension at a dose of 250 to 500 mg BID for 7 to 14 days in the treatment of mild/moderate to severe/complicated UTI.

B. Overview of Materials Utilized in the Review

Material Submitted Electronic Data, including SAS transport files
 \\Cdsesub1\n21554\N_000\2002-10-29

Material Reviewed Electronic Data, including SAS transport files
 \\Cdsesub1\n21554\N_000\2002-10-29

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A DSI audit was not requested for this trial.

Reviewer's Comment: A routine DSI audit was not felt to be necessary for this NDA since Cipro XR was approved for a similar indication (NDA 21-473) on December 13, 2002. No discrepancies were noted in the clinical data to warrant a directed (for-cause) inspection.

D. Evaluation of Financial Disclosure

The applicant obtained certification from each investigator and sub-investigator who enrolled patients in the Phase III study. No investigator or sub-investigator had any disclosable information to reveal.

V. Integrated Summary of Efficacy (ISE)

A. Brief Statement of Efficacy Conclusions

The applicant conducted one pivotal Phase III trial in the United States and Canada (Protocol 100275) which documents the efficacy of Cipro XR compared to ciprofloxacin immediate release (Cipro BID) oral tablets for complicated urinary tract infection (cUTI) and acute uncomplicated pyelonephritis (AUP).

The results of supportive data provide further evidence of the efficacy of Cipro XR therapy in treatment of cUTI and AUP.

B. General Approach to Efficacy Review

The US Phase III trial (Protocol 100275) is considered pivotal. A synopsis is provided below and the complete clinical review can be found in Appendix 1.

C. Efficacy Conclusions

Cipro XR was evaluated for the treatment of complicated urinary tract infections (cUTI) and acute uncomplicated pyelonephritis (AUP) in a randomized, double-blind, controlled clinical trial conducted in the US and Canada. The study enrolled 1,042 patients and compared Cipro XR (1000 mg once daily for 7 to 14 days) with immediate-release ciprofloxacin (500 mg twice daily for 7 to 14 days). The primary endpoint for this trial is bacteriologic eradication, of the baseline organism(s) with no new infection or superinfection, at 5 to 11 days post-therapy.

In the applicant's analysis, bacteriologic eradication in AUP and cUTI patients combined in the valid for efficacy (Per Protocol) population is 88.8% (183/206) in the Cipro XR group and 85.2% (85.2%) in the Cipro BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (-2.4%, 10.3%) lies above -10%, indicating the non-inferiority of Cipro XR 1000 mg QD compared to Cipro 500 mg BID.

There are several problems with the applicant's analysis of bacteriologic eradication in cUTI and AUP patients combined in the Per Protocol (PP) population.

- First, there is a difference in the treatment effect between patients with AUP and cUTI. The eradication rates for the AUP patients are higher in the Cipro BID group (98.1%) than in the Cipro XR group (87.5%). In contrast the eradication rates for cUTI patients are higher in the Cipro XR group (89.2%) than in the ciprofloxacin BID group (81.4%). The *P* value from the Breslow-Day test for treatment-by-infection interaction is significant at 0.008, indicating that the treatment effect is different between AUP patients and cUTI patients. The Division does not consider it appropriate to pool efficacy results for cUTI and AUP patients due to the significant treatment-by-infection interaction.
- Second, although not specified by the applicant, the Division defined a Modified-to-Treat (MITT) population that includes all patients with a causative organism(s) isolated at baseline and who received at least one dose of study medication. When the MITT population is examined along with reasons for exclusion from the PP population, there are significantly more patients in the Cipro XR group (40%, 136/342) than in the Cipro BID group (29%, 95/324) that had been excluded from the PP population. Exclusions from the PP population are primarily a result of premature discontinuations, which are primarily due to adverse events (2.9% versus 1.7%, respectively) and no valid test-of-cure (TOC) urine culture or lost to follow-up (7.7% versus 4.6%, respectively). A differential rate in exclusion may bias the results of any analysis using this population.

Therefore, the bacteriologic eradication rates for AUP and cUTI were calculated separately by the FDA statistical reviewer and reported for both the MITT and PP populations. Since in the applicant's analysis random assignment of treatment was stratified by infection type, the calculation of the difference in eradication rates between treatment groups for each stratum alone must be adjusted for multiple comparisons (i.e., 97.5% confidence intervals). The bacteriologic eradication rates and their corresponding 97.5% confidence intervals for the differences between rates (Cipro XR minus Cipro BID) for AUP and cUTI patients, at the TOC visit are given in the following table for both the MITT and PP populations.

*Appears This Way
On Original*

TABLE 4
Bacteriologic Eradication at TOC (+5 to +11 Days)
in AUP and cUTI Patients

	MITT*		PP**	
	n/N (% of Patients)	[95% CI of the Difference]	n/N (% of Patients)	[95% CI of the Difference]
AUP Patients				
Cipro XR	47/71 (66.2%)	[-26.8, 6.5]	35/40 (87.5%)	[-34.8, 6.2]
Cipro BID	58/76 (76.3%)		51/52 (98.1%)	
cUTI Patients				
Cipro XR	160/271 (59.0%)	[-13.5, 5.7]	148/166 (89.2%)	[-0.7, 16.3]
Cipro BID	156/248 (62.9%)		144/177 (81.4%)	

* Patients excluded from the Modified Intent-to-Treat group are those with no causative organism at baseline and those who did not receive study drug.

** Patients excluded from the Per Protocol group are those with no causative organism(s) at baseline, no valid TOC urine culture, inclusion/exclusion criteria violation, organism resistant to study drug, protocol violation, non-compliance with dosage regimen, did not receive study drug, inadequate duration of treatment, post-therapy antibiotics, and concomitant antimicrobial therapy.

For AUP patients, the 97.5% confidence interval for the treatment difference in bacteriologic eradication rates is below -10% in both the MITT and PP populations, indicating the conditions for non-inferiority of Cipro XR compared to Cipro BID were not met. For cUTI patients, the 97.5% confidence interval of difference is above -10% in the MITT and PP populations (and almost above zero in the PP population), indicating non-inferiority of Cipro XR compared to Cipro BID (and a trend toward superiority in one analysis).

VI. Integrated Summary of Safety (ISS)

A. Brief Statement of Safety Conclusions

Overall, there are no clinically meaningful differences in the safety profile of Cipro XR compared to Cipro BID. Of note, however, is the difference in discontinuations due to adverse reactions in the Cipro XR group (5.4%, 28/517) compared to Cipro BID (3.7%, 19/518). The most common reasons for discontinuation, regardless of attributability to study drug, in the Cipro XR group are dizziness and nausea/vomiting [both 25% (5/28)] and headache [11% (3/28)]. In the Cipro BID group the most common reasons for discontinuation are nausea/vomiting and LFT abnormalities [both 21% (4/19)] and diarrhea [11% (2/19)]. No patient discontinued due to dizziness in the Cipro BID group.

B. Description of Patient Exposure

A total of 1042 patients were enrolled in Study 100275 at 100 investigative centers in the US and Canada. Of the 1042 enrolled patients, 521 were assigned randomly to treatment with Cipro XR 1000 mg once daily and 521 were assigned randomly to treatment with Cipro 500 mg twice daily. Seven patients (4 in the Cipro XR group and 3 in the Cipro BID group) were not included in the valid for

safety population because study drug administration in these patients could not be documented. Thus, there were 517 (408 cUTI and 109 AUP) patients in the Cipro XR group and 518 (407 cUTI and 111 AUP) patients in the Cipro BID group valid for the analysis of safety. All patients valid for safety received treatment over the course of 5 to 15 days, with a mean duration of treatment of 12 days.

C. Specific Findings of the Safety Review

Of the 1042 patients enrolled in the study, 1035 received at least one dose of study drug and are valid for the analysis of safety (517 in the Cipro XR group and 518 in the Cipro BID group). The proportion of patients who experienced at least one adverse event (31.9%) is the same in both treatment groups.

More patients in the Cipro XR group (28 patients or 5.4%) than in the Cipro BID group (19 patients or 3.7%) discontinued study drug due to an adverse event. The most common reasons for discontinuation, regardless of attributability to study drug, in the Cipro XR group are dizziness and nausea/vomiting [both 25% (5/28)] and headache [11% (3/28)]. In the Cipro BID group the most common reasons for discontinuation are nausea/vomiting and LFT abnormalities [both 21% (4/19)] and diarrhea [11% (2/19)]. No patient discontinued due to dizziness in the Cipro BID group.

The most common adverse events in both treatment groups are those occurring in the digestive system [14% (71/517) for Cipro XR and 13% (67/518) for Cipro BID]. The incidence of adverse events for each body system is similar between treatment groups, except for the nervous system. Six percent (6%) of patients in the Cipro XR group (30/517) experienced at least one adverse event involving the nervous system compared with 4% (20/518) in the of Cipro BID group. The events primarily responsible for this difference are dizziness (16 patients [3%] in the Cipro XR group versus 10 patients [2%] in the Cipro BID group), and abnormal dreams, depression, hallucinations, stupor, thinking abnormal, tremor, and hypesthesia (1 patient for each [$<1\%$] versus 0 patients [0%], respectively).

Most patients in both treatment groups who experienced adverse events had events that were assessed by the investigator as mild or moderate in intensity. Adverse events that occur in at least 2% of patients treated with Cipro XR include nausea (5%), headache (3%), diarrhea (3%), vomiting (3%), dizziness (3%), dyspepsia (2%), and vaginal moniliasis (2%). Cipro BID has a similar profile of adverse events occurring in at least 2% of patients, with a slightly higher incidence of headache (5%).

Study drug-related (possible or probable relationship) adverse events were reported in 13% (68/517) of patients in the Cipro XR group and 14% (70/518) of patients in the Cipro BID group. Those occurring in 2% or more of patients in either treatment group include headache, nausea, diarrhea, dizziness, and vaginal moniliasis.

A small proportion of patients had events that were assessed by the investigator as severe in intensity. Seven percent (35/517) of all valid for safety patients in the Cipro XR group and 5% (28/518) in the Cipro BID group experienced at least one adverse event assessed by the investigator as severe in intensity. The number of

severe adverse events represents 14.6% (50/342) and 12.8% (39/304), respectively, of the total number of adverse events reported.

Four patient deaths were reported during the study (3 in the Cipro XR group and one in the Cipro BID group). All four patients were in the older age range (76 to 95 years), had a diagnosis of cUTI with one underlying condition, and had other concurrent medical conditions requiring concomitant medications. In all cases, the adverse event resulting in death was judged by the investigator to be of unlikely or no relationship to study drug and the FDA reviewer concurred.

Patients experiencing non-fatal serious adverse events (SAEs) is 5% in both treatment groups, (28/517 and 24/518, respectively). All SAEs reported in the Cipro XR group were judged by the investigators to be unlikely or not related to study drug.

In the two treatment groups, the incidence of clinically significant ($>1.8 \times \text{ULN}$) abnormalities in SGOT and SGPT is the same (2%). For abnormalities in SGOT and SGPT that are $>3 \times \text{ULN}$, the incidence is 1% in the Cipro XR group and 2% in the Cipro BID group. Two patients ($<1\%$) in the Cipro XR group had liver function test abnormalities that were reported as adverse events. In both cases, the events resolved and did not require discontinuation of study drug. Seven patients (1%) treated with Cipro BID had abnormal liver function test results that were reported as adverse events. In 4 of these 7 patients, the liver function test abnormalities were a reason for discontinuation of study medication. Only one of the 4 patients in the Cipro BID group who discontinued prematurely for liver function test abnormalities had all tests within the normal range at baseline.

The incidence of other laboratory test abnormalities is low and comparable between the two treatment groups. Descriptive statistics of the change from baseline in laboratory test results does not reveal any trends that appear to be uniquely associated with Cipro XR treatment.

Overall, there are no clinically meaningful differences in the safety profile of either treatment on the basis of age, sex, or race.

VII. Dosing, Regimen, and Administration Issues

The dosage regimen of Cipro XR 1000 mg administered daily for 7 to 14 days for the treatment of cUTI and AUP is based on Phase I studies of this formulation and the approved labeling for conventional ciprofloxacin tablets. The current recommended dosage for ciprofloxacin tablets in the treatment of mild/moderate to severe/complicated urinary tract infections is 250 to 500 mg BID for 7 to 14 days. The Phase I studies for Cipro XR (Studies 10324 and 10339) indicate that the ciprofloxacin AUC attained following the oral administration of Cipro XR 1000 mg tablets every 24 hours is similar to the values attained following the oral administration of conventional ciprofloxacin 500 mg tablets every 12 hours (16.5 mg*h/L versus 16.0 mg*h/L, respectively, in Study 10324; and 15.4 mg/h/L versus 14.8 mg*h/L, respectively, in Study 10339). The C_{max} of Cipro XR 1000 mg given every 24 hours is about 46% higher than the C_{max} for Cipro 500 mg tablets given every 12 hours.

VIII. Use in Special Populations

A. Evaluation of Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity

1. Efficacy

Age

For patients treated with Cipro XR, the bacteriologic eradication rates are lower in patients less than 65 years of age [85.0% (85/100)] compared to those 65 years of age and older [92.4% (98/106)] at the TOC visit. Less efficacy in the younger patients may be a result of the lower bacteriological response in AUP patients [87.5% (935/40)] compared to cUTI patients [89.2% (148/166)]. Patients treated with Cipro XR in the AUP sub-group are younger (mean age 41 years) compared with cUTI (mean age 64 years).

Although younger patients treated with Cipro XR have lower eradication rates [85.0% (85/100)] than older patients treated with Cipro XR, the efficacy in this age group is similar to patients treated with Cipro BID [84.1% (90/107)]. Patients receiving Cipro BID responded similarly, regardless of age [84.1% (90/107) eradication for those < 65 years and 86.1% (105/122) for those ≥ 65 years].

In the Reviewer's opinion, differences seen in bacteriologic eradication between younger and older patients is not considered clinically meaningful and no adjustments to the dosing of Cipro XR are warranted based on age.

Sex

Male patients [92.0% (81/88)] have a higher bacterial eradication rate than female patients [86.4% (102/118)] treated with Cipro XR at the TOC visit. The reverse situation is true for Cipro BID where female patients [89.8% (114/127)] have a higher eradication rate than male patients [79.4% (81/102)]. The difference in the Cipro XR group appears to be due to a higher number of female patients with superinfections and new infections.

Although the female patients treated with Cipro XR have lower eradication rates [86.4% (102/118)] than male patients treated with Cipro XR, the efficacy in this group is similar to female patients treated with Cipro BID [89.8% (114/127)] and higher than male patients treated with Cipro BID [79.4% (81/102)].

In the Reviewer's opinion, differences seen in bacteriologic eradication between male and female patients is not considered clinically meaningful and no adjustments to the dosing of Cipro XR are warranted based on sex.

Race

Most of the valid for efficacy patients are Caucasian [79% (345/435)]. Among patients who are not Caucasian, most are categorized as Black or Hispanic [20% (88/435)]. Less than 1% of patients in each treatment group are Asian. Bacteriologic eradication rates for both Cipro XR and Cipro BID appear similar for Caucasian and Black patients at the TOC visit. Hispanic patients appear to have higher eradication rates. There are too few Asian patients in the study to make an assessment on eradication.

In the Reviewer's opinion, differences seen in bacteriologic eradication between Caucasian, Black, and Hispanic patients are not considered clinically meaningful and no adjustments to the dosing of Cipro XR are warranted based on race.

2. Safety

Age

The overall incidence rates of adverse events are similar across age groups (< 65 years, 65-74 years, and ≥ 75 years) in patients within each treatment group. For both the Cipro XR and Cipro BID group, patients aged 65-74 years experienced nausea less frequently than those younger or older. More patients younger than 65 years of age in the Cipro XR group reported vomiting [4% (12/271)] than did patients in the same age category treated with Cipro BID [<1% (2/255)]. The incidence of dizziness in patients 75 years of age or older is slightly higher in the Cipro XR group [4% (6/149)] as compared to the Cipro BID group [1% (2/159)]. The incidence rates of other adverse events for both treatment groups across age groups are similar.

In the Reviewer's opinion, differences seen in adverse events between younger and older patients treated with Cipro XR are not considered clinically meaningful and do not warrant reporting by age in the product labeling.

Sex

Within each sex, the event rates are similar between Cipro XR and Cipro BID patients. Overall, female patients have higher event rates than male patients [34% (102/298) for females vs. 29% (102/299) for males]. Overall, female patients have higher rates of nausea and diarrhea [nausea: 6% in both Cipro XR (19/298) and Cipro BID (18/299) groups; diarrhea: 4% (11/298) in Cipro XR and 3% (8/299) in Cipro BID] than the male patients [nausea: 2% in both Cipro XR (5/219) and Cipro BID (5/219) groups; diarrhea: 2% (4/219) in Cipro XR and 1% (3/219) in Cipro BID]. Of the Cipro XR treated patients more females reported vomiting [4% (12/298)] than males [<1% (2/219)].

In the Reviewer's opinion, differences seen in adverse events between male and female patients treated with Cipro XR are not considered clinically meaningful and do not warrant reporting by sex in the product labeling.

Race

Adverse event rates generally are consistent across subgroups. The number of patients with any adverse event is comparable between the two treatments for Caucasian: 31% (129/410) for Cipro XR and 33% (138/414) for Cipro BID

and Hispanic 27% (13/48) for Cipro XR and 30% (16/53) for Cipro BID patients. Black patients treated with Cipro XR have a higher incidence of adverse events [38% (21/55)] compared with Black patients treated with Cipro BID [23% (11/48)]. This is due primarily to adverse events attributed to the urogenital system: 16% (9/55) in Cipro XR-treated patients versus 8% (4/48) Cipro BID-treated patients.

Within the Cipro XR group, more Hispanic patients developed nausea, headache, or vomiting than did black or Caucasian patients. In the Cipro BID group, Hispanic patients have a higher incidence of abdominal pain than did patients of the other two racial groups. There are no other notable differences between the two treatment groups by race. Overall, there are no clinically meaningful differences in the incidence of adverse events across the three racial groups (i.e., Caucasian, Black, and Hispanic). Conclusions cannot be made for patients categorized as Asian or American Indian because their numbers are too small for a meaningful comparison.

B. Pediatric Program

Pursuant to 21 CFR 314.55 (c), the applicant requests a full waiver of the assessment of the efficacy and safety of Cipro XR 1000 mg tablets in the pediatric population.

Cartilage lesions have been demonstrated in the weight bearing joints of immature dogs given ciprofloxacin. This is a class effect of all quinolones. The warnings section of the proposed package insert cautions against the use of this product in pediatric patients. The applicant believes that definitive statements concerning the manifestation of this effect in humans cannot be made presently.

[

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Ciprofloxacin is an extremely bitter drug substance. The applicant states that development of an oral liquid formulation for twice daily dosing was extremely difficult, and they believe that "reasonable attempts", to produce an oral liquid formulation for once-daily dosing at this strength would be impossible. In addition, Cipro XR tablets are quite large. They believe a smaller once daily tablet for the pediatric population will still be too large for many children to swallow. Finally, they do not believe the development of such a smaller tablet will provide a "meaningful therapeutic benefit" for pediatric patients over existing treatments, as there already exists an oral liquid dosage form of ciprofloxacin available for use for pediatric patients.

In summary, the applicant requests a full waiver for the assessment in pediatric patients for Cipro XR (NDA 21-554). [

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Reviewer's Comment: The FDA's Pediatric Rule at 21 CFR 314.55 was challenged in court and on October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling.

C. Data in Other Populations

Pediatric patients (< 18 years) and patients with significant renal impairment (serum creatinine >3.0 mg/dL or creatinine clearance <30 mL/min*1.73 m²) or hepatic impairment (baseline SGOT or SGPT and/or total bilirubin greater than 3 times the upper limit of normal), and pregnant women were excluded from the Cipro XR development program. Therefore it is not possible to comment on the efficacy or adverse event profile in these populations.

IX. Conclusions, Recommendations, and Labeling

A. Conclusions Regarding Efficacy and Safety

In this submission, the applicant demonstrates the activity of 7 to 14 days of treatment with 1000 mg of Cipro XR in the treatment of patients with complicated urinary tract infection (cUTI) and acute pyelonephritis (AUP). The efficacy of Cipro XR is compared to a FDA-approved regimen consisting of immediate-release ciprofloxacin 500 mg tablets twice daily (Cipro BID) for 7 to 14 days. The Cipro BID regimen is an acceptable comparator since it is approved for severe/complicated urinary tract infections at a dose of 250 to 500 mg twice daily for 7 to 14 days.

B. Recommendations on Approvability

In summary, Cipro XR is safe and effective for the treatment of patients with cUTI in patients with susceptible organisms, including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*^a, and *Proteus mirabilis*. In addition, Cipro XR is safe and effective for the treatment of patients with AUP in patients with susceptible organisms, including *Escherichia coli*. The recommendation is for approval of Cipro XR 1000 mg once daily for 7 to 14 days for cUTI and AUP.

^a Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

C. Labeling

1. Changes to Applicant's Proposed Label

The major labeling changes and means of resolution are indicated below by affected section(s) of the label:

Microbiology, Indications and Usage, and Clinical Studies

The applicant originally included *Escherichia coli* and *Pseudomonas aeruginosa* in the "Indications and Usage" section and in the efficacy table in the "Clinical Studies" section of the package insert. At a teleconference on July 10, 2003, the Division asked the applicant to provide information to support the inclusion of these two organisms in the table, since there are less than 10 isolates for each. On July 29, 2003 the applicant submitted the requested information. They indicated that they were withdrawing the proposal to include *Escherichia coli* in the "Indications and Usage" and "Clinical Studies" section and will shift the organism to the "second list" in the "Microbiology" section of the package insert.

Regarding the inclusion of *P. aeruginosa* in the XR label, the applicant justified their position with data to support the following: (1) immediate-release (IR) ciprofloxacin is indicated for cUTIs, including those caused by susceptible strains of *P. aeruginosa*, (2) an antimicrobial agent selected to treat cUTI should achieve adequate concentrations at the site of infection. Cipro XR 1000 mg tablets have an absolute bioavailability of up to 90% and a relative bioavailability of 98% when compared to the IR formulation. Plasma concentrations are about 40% to 70% greater than the concentrations achieved with 500 mg BID of the immediate-release formulation. In the urine, the XR formulation of ciprofloxacin (1000 mg) achieves significantly higher concentrations of ciprofloxacin than the immediate release formulation (500 mg BID) for up to 12 hours following a dose. Concentrations of both formulations in the urine remain in excess of the MIC values of susceptible pathogens throughout the dosing interval, (3) surveillance data shows that 75% of *P. aeruginosa* isolates from UTIs analyzed between Jan 1st and December 31st 2002, were susceptible to ciprofloxacin, and (4) nine of the 14 *P. aeruginosa* isolates identified in the pivotal trial (100275) were susceptible to ciprofloxacin. All nine were clinically cured and bacteriologically eradicated.

The applicant concludes that a combination of the microbiological data (MICs) for susceptible isolates of *P. aeruginosa* along with the achievable concentrations of the drug in plasma and urine, supports Cipro XR as an appropriate drug to select for the treatment of cUTI caused by susceptible strains of *P. aeruginosa*.

The applicant also indicated that they would be amenable to conduct a Phase IV study to gather additional isolates of *P. aeruginosa*, similar to what the Division requested of the applicant when the Division approved *Staphylococcus saprophyticus* in uUTI (Cipro XR 500 mg, NDA 21-473), if the Division would grant them *P. aeruginosa* in the label.

The reviewer accepts the applicant's rationale for inclusion of *P. aeruginosa* in the label, based on the pharmacokinetic and susceptibility data provided. In addition, the applicant will be requested to obtain information on additional isolates of *P. aeruginosa* as a Phase IV commitment.

Adverse Events

The applicant originally proposed combining the data in the adverse events section for the 500 mg and 1000 mg XR tablets. The rate of adverse events leading to discontinuation was reported as 1.8%, which is an average of 0.2% for the 500 mg XR tablet and 2.3% for the 1000 mg XR tablet. Therefore, the reviewer requested the applicant report the rates of discontinuation due to AEs and the most common AEs leading to discontinuation separately for the two doses. The rationale behind this request is that the patient populations (i.e., uUTI versus cUTI/AUP), duration of treatment (3 days versus 7-14 days), as well as treatment doses (500 mg versus 1000 mg) are different and may be contributing to the difference in discontinuation rates. In addition to separating the information by dose and indication, the applicant was asked to include information on discontinuation due to AEs from the comparator arms (i.e., ciprofloxacin immediate release 250 mg BID and 500 mg BID, respectively).

Clinical Trials

The description of the pivotal study (100275) was modified by the reviewer from the applicant's proposal in three ways:

- In the trial there are a disproportionate rate of exclusion from the PP population for the two treatment groups. The Division feels the results of the MITT analysis should be represented in the label to adequately describe the study. Therefore, results of the MITT analysis are included, in addition to the PP analysis proposed by the applicant.
- In the trial there is also a significant treatment by infection interaction, such that the Division does not consider it appropriate to pool bacteriologic results for the cUTI and AUP subgroups. Therefore, bacteriologic eradication rates, and corresponding confidence intervals, in both the MITT and PP populations are reported separately for the cUTI and AUP subgroups and not reported for the combined sub-groups, as proposed by the applicant. The Division allowed the clinical success rates to be reported for the combined cUTI and AUP subgroups, in the PP population, because there was no significant treatment by infection interaction for this endpoint.
- Cipro XR achieves lower rates of bacteriologic eradication in the AUP subgroup and higher rates in cUTI subgroup compared to Cipro BID. By definition, in this study bacteriologic failures include patients with persistence, new infections, and superinfections. Therefore, a narrative descriptions of the number of patients failing due to persistence, new

infection, or superinfection and the causative pathogen(s) are added for AUP and cUTI patients in the PP population.

2. Other Potential Labeling Issues Related to Safety

Three potentially serious adverse events (occurring in less than 1% of patients) have been added to the label. These adverse events were not seen with the 500 mg XR dose and are as follows: "liver function tests abnormal", "bradycardia", and "syncope". In order to determine the clinical relevance of the event, the reviewer investigated each AE. Patient summaries/narratives are included below. The reviewer does not feel that these adverse events are clinically relevant and also do not represent a "signal" for more serious cardiac or hepatic toxicity.

- **Liver Function Tests Abnormal:** Two patients in the Cipro XR group had liver function test abnormalities that were reported as adverse events. For one patient the liver enzyme levels were below 1.8x ULN and were thought to be possibly related to study drug. In the other patient the liver enzyme levels were 3x ULN and 4.8x ULN for SGOT and SGPT, respectively, and not believed to be related to study drug. In both cases, the events resolved and did not require discontinuation of study drug.
- **Bradycardia:** A 20-year-old male patient had a past medical history of a C6-7 spinal cord injury, and intermittent bradycardia, since his the injury 3 months earlier. On the second day of study drug treatment, he experienced bradycardia, dizziness and double vision. The study drug was immediately discontinued and IV fluids (D5W, 0.45NS) were administered in the office for the bradycardia. All three events resolved the next day and were considered possibly related to study drug.
- **Syncope:** On the first day of study drug treatment a 72-year-old female patient reported lightheadedness. No action was taken and the event resolved that day. Three days later, she experienced a faint feeling. The study drug was permanently discontinued and the event improved. This patient withdrew consent for further treatment. Both events were considered possibly related to study drug.

Joette M. Meyer, Pharm.D.
Clinical Reviewer, DSPIDP, ODE IV, CDER

Concurrence:
HFD-590/TLMO/RocaR
HFD-590/DivDir/AlbrechtR

APPENDIX 1 – INDIVIDUAL STUDY REVIEW FOR STUDY 100275

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Title

Prospective, Randomized, Double Blind, Multi-Center Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once-Daily (QD) [] (Cipro MR*) Tablets 1000mg versus Conventional Ciprofloxacin 500mg Tablets BID in the 7-14 Day Treatment of Patients with Complicated Urinary Tract Infections (cUTI) or Acute Uncomplicated Pyelonephritis (AUP).

*The product was subsequently renamed Cipro XR

Protocol Number

100275

Study Initiation

April 15, 2001

Study Completion

July 11, 2002

All the following tables in this review are reproductions from the applicant's submission, unless otherwise noted.

I. Investigators and Study Administrative Structure

This is a multicenter study involving 100 investigative sites in the United States and Canada. The study was monitored by a contract research organization (CRO), [], in accordance with GMP guidelines and Standard Operating Procedures (SOP) for Bayer and []. Monitoring visits were done to ensure compliance with the protocol, to review source documents and case report forms (CRF), and to assess drug accountability.

Analysis of routine blood, serum pregnancy, and urine laboratory samples, urine cultures, and susceptibility testing were processed and analyzed at []

Screening urine pregnancy tests for women of childbearing potential were conducted at the study sites.

The design for the pivotal study was guided by following two FDA documents:

- Points to Consider: Urinary Tract Infections. 1997
- Draft Guidance for Industry: Complicated Urinary Tract Infections and Pyelonephritis - Developing Antimicrobial Drugs for Treatment. July 1998

The applicant also gave consideration to the other following documents when designing this study: the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines (1993), the Committee on Proprietary Medicinal Products' (CPMP) Note for Guidance on Evaluation of New Antibacterial Medicinal Products (1998), and the Infectious Disease Society of America (IDSA) Practice Guidelines Committee publication (1999).

II. Study Objectives

The primary objective of this study is to determine if ciprofloxacin extended-release (Cipro XR) 1000 mg orally once daily for 7 to 14 days is non-inferior to immediate-release ciprofloxacin (Cipro) 500 mg orally twice daily for 7 to 14 days in the treatment of patients with complicated urinary tract infection (cUTI) or acute uncomplicated pyelonephritis (AUP). The primary efficacy variable is bacteriological outcome at the test-of-cure (TOC) visit (+5 to +11 days after the last dose of study drug)

Secondary objectives are to compare the clinical response rate between treatments at the TOC visit, and to compare bacteriological and clinical response rates at the late follow-up visit (+28 to +42 days after the last dose of study drug).

III. Investigational Plan

This is a prospective, randomized, double blind, multicenter, Phase III clinical trial conducted at 100 investigative centers in North America. Men and non-pregnant women who were 18 years of age or older and who had a cUTI or AUP were eligible for enrollment. A total of 1036 consenting qualified patients were expected to participate in order to obtain 202 evaluable patients in each treatment arm.

Reviewer's Comment: The original protocol specified a total of 408 patients required for enrollment in order to obtain 153 evaluable patients in each treatment arm. Protocol Amendment 1 changed these numbers to 886 patients and 332, respectively. Protocol Amendment 5 increased the total number of patients enrolled to 948 to obtain 237 evaluable patients per treatment arm. Finally, Protocol Amendment 7 increased the numbers to 1036 patients total and 202 evaluable patients per arm.

After meeting all inclusion/exclusion criteria and providing written informed consent, patients were stratified based on diagnosis (Stratum I: acute uncomplicated pyelonephritis; Stratum II: complicated UTI) and assigned randomly to treatment with either Cipro XR 1000 mg once daily or Cipro 500 mg twice daily for 7 to 14 days.

Patient assessments were performed at the following visits:

- Screening visit (within 48 hours before the first dose of study drug);
- During-therapy visit (Day 3 to 5 of therapy)
- TOC visit (Day +5 to +11 post-treatment)
- Late follow-up visit (Day +28 to +42 post-treatment)
- If applicable: premature-discontinuation-of-study-drug visit, or a post-alternative-treatment visit (Day +2 to +4 post-treatment).

The efficacy of the study drug was determined at the TOC visit on the basis of the clinical and bacteriological outcome of the patient.

The clinical outcome was based on serial examinations of the patient to determine the effect of therapy on the signs and symptoms of the infection. All pertinent laboratory tests or procedures that reflect the course of the urinary tract infection (UTI) were also assessed. Absence or reduction of pyuria, dysuria, frequency,

urgency, suprapubic pain, fever (>38°C/100.4°F orally), chills, flank pain, nausea and/or vomiting, or costo-vertebral angle (CVA) tenderness on examination were used to assess the clinical response.

The bacteriological outcome was based on the results of urine cultures obtained before the start of therapy, at the TOC visit, at the late follow-up visit and at premature discontinuation (if applicable). The safety of study drug treatment was monitored by clinical observations including the determination of vital signs, adverse event monitoring, and laboratory assessments of hematologic, liver, and renal functions.

IV. Inclusion Criteria

- Men or non-pregnant women, 18 years of age or older, with a suspected cUTI or AUP.
- Women of childbearing potential must use two highly reliable methods of contraception during exposure to study drug (e.g., if a woman is on oral contraceptive, she is required to use a barrier method of contraception as well).
- For cUTI, patients must present with one or more of the following signs or symptoms:
 - dysuria
 - urgency
 - frequency
 - suprapubic pain
 - back pain
 - flank pain
 - CVA pain and tenderness
 - fever (>38° C/100.4° F orally) with or without chills

AND at least one or more underlying conditions, such as:

- indwelling urinary catheter
 - 100 mL of residual urine after voiding
 - neurogenic bladder
 - obstructive uropathy due to nephrolithiasis, tumor or fibrosis
 - urinary retention in men, possibly due to benign prostatic hypertrophy
- For AUP, patients must present with clinical signs and symptoms of an ascending UTI, manifested by all 3 of the following: fever (>38°C/100.4°F orally), chills and flank pain.

In addition, patients also may have CVA tenderness and nausea. Symptoms of lower UTI such as dysuria, nocturia, frequency, urgency, suprapubic or lower back pain also may be present.

- Patients also must have a positive pre-treatment, clean-catch, midstream urine culture, defined as $\geq 10^5$ CFU/mL for a causative pathogen, within 48 hours of enrollment.

If more than 1 pathogen is identified, each should be present at a colony count $\geq 10^5$ CFU/mL to be included in the analysis. In catheterized patients, the urine sample may be obtained from the catheter using a sterile technique and not from the Foley bag. In addition, patients should have blood culture specimens (two sets from different sites) obtained simultaneously with the urine specimen at the time of enrollment. If two or more pathogens grow at $\geq 10^5$ CFU/mL from the baseline urine culture sample of a catheterized patient, all isolates will be considered to be contaminants (i.e., nonevaluable), unless the same pathogen is isolated from a simultaneously obtained blood culture sample. If the same pathogen grows in the urine at $\geq 10^5$ CFU/mL and also is isolated from the blood, then it will be considered to be an evaluable pathogen.

- Patients must also have pyuria, defined as ≥ 10 leukocytes/mm³ in unspun pre-treatment urine specimens or >5 WBC/hpf in spun pre-treatment urine specimens. The sedimentation method or slide method of assessing urinary leukocytes is acceptable. The causative pathogen must be susceptible to ciprofloxacin as determined by *in vitro* susceptibility testing.

V. Exclusion Criteria

Patients will not be enrolled if they:

- Have a history of allergy to quinolones
- Are unable to take oral medication
- Have prostatitis or epididymitis
- Have an intractable infection requiring >14 days of therapy
- Have an uncomplicated UTI
- Have a renal transplant
- Have ileal loops or vesico-ureteral reflux
- Have a ciprofloxacin-resistant pathogen upon urine or blood culture
- Have received systemic antimicrobial therapy within 48 hours prior to enrollment
- Have a neutrophil count $<1000/\text{mm}^3$, CD4 $<200/\text{mm}^3$ or other conditions associated with significant depression in host defense (HIV testing was not mandatory)
- Have a requirement for concomitant systemic antibacterial therapy with agents not specified in this protocol
- Have significant liver impairment (baseline SGOT or SGPT and/or total bilirubin) greater than 3 times the upper limit of normal
- Have significant renal impairment (serum creatinine >3.0 mg/dL or creatinine clearance <30 mL/min*1.73 m²)
- Have a history of tendinopathy associated with fluoroquinolones;
- Are pregnant, nursing or in whom pregnancy could not be excluded or unreliable contraception was being used; diagnosed with a rapidly fatal underlying disease (death expected within 6 months)
- Have a requirement for concomitant administration of sucralfate or divalent and trivalent cations, such as iron or antacids containing magnesium, aluminum or calcium; previously enrolled in this clinical study; taken an investigational drug in the last 30 days.

VI. Patient Removal

A patient may have been withdrawn from the study at any time at the discretion of the investigator or if a patient withdrew consent. If a patient did not show improvement after three days (i.e., therapeutic failure), if a serious toxic or allergic reaction occurred, or if a superinfection developed, study drug therapy was discontinued and appropriate alternative therapy was instituted. Before alternative antimicrobial drugs were given, however, the patient was fully evaluated and appropriate laboratory tests including cultures were performed. In addition, the investigator may have withdrawn patients from the trial for reasons such as poor compliance (taking < 80% of study medication), an elevated pre-treatment laboratory test result, deterioration in a concurrent clinical condition precluding continuation of study medication, or protocol violation.

The study could be terminated if, in the opinion of the investigator and/or sponsor, continuation would represent an unacceptable risk to the patients, or if the status of ciprofloxacin XR development by the sponsor had changed such that the study would no longer be a necessary part of the clinical program.

If, during the course of study drug therapy, study drug was discontinued prematurely for any reason, a premature discontinuation of therapy visit was required. All end-of-therapy assessments were to be performed at this visit. In addition, a clean-catch midstream urine sample was to be obtained and sent to the central laboratory for culture and susceptibility testing.

VII. Treatments and Blinding

Patients received Cipro XR 1000 mg tablets orally once daily or Cipro 500 mg tablets orally twice daily for 7 to 14 days. Study medication was provided in a package containing 2 bottles to maintain the double blind design of the study.

Bottle #1 (the smaller bottle): 14 tablets of Cipro XR 500 mg or matching placebo
Bottle #2 (the larger bottle): 28 tablets of Cipro 500 mg or matching placebo

For the first daily dose the patient was instructed to take 2 tablets: one tablet from Bottle #1 and one tablet from Bottle #2. For the second daily dose the patient was instructed to take one tablet from Bottle #2 and none from Bottle #1. Thus, in a 24-hour dosing period, the patient took a total of 3 tablets.

All doses of study medication were to be taken with at least 120 mL (4 oz.) of water and without regard to meals.

All personnel associated with drug administration (including study and treating health care providers), patients, study monitors, and Bayer medical research personnel were blinded to the treatment assignment.

In the event of an emergency, the random code could be broken; however, the investigator was instructed to make every attempt to contact Bayer prior to breaking the code. If the code was broken, Bayer was notified by telephone or facsimile within 48 hours. Regardless of the reason, once the blind for any patient was broken, that patient was not valid for the primary efficacy analysis. In the event the blind was

broken, the date and reason for the code break was documented and signed by the investigator in a report to the applicant.

VIII. Method of Patient Assignment to Treatment Group

Patients who met all enrollment criteria were stratified based on the presence or absence of AUP as follows:

- Stratum I: Patients with acute uncomplicated pyelonephritis
Stratum II: Patients without acute uncomplicated pyelonephritis but with a diagnosis of cUTI

Following stratification, patients were assigned randomly to one of two drug treatment groups (i.e., Cipro XR 1000 mg once daily or Cipro 500 mg twice daily) in accordance with a computer-generated random code provided by the applicant. Patients were assigned from a single stream code of study numbers. The investigators, study monitors, and patients all were blinded to the random code assignment.

Randomization and initiation of study drug treatment is permitted before the culture report became available.

Reviewer's Comment: In order to obtain an indication for AUP, in addition to cUTI, an adequate number of AUP patients must be studied. According to the Draft Guidance for Industry, the minimum number of AUP patients required is 30 patients per investigational treatment per study. In this study, there are 40 AUP patients in the valid for efficacy population treated with Cipro XR. Therefore, the applicant is eligible to receive an AUP indication based on number of patients. In addition, minimum efficacy requirements for Cipro XR will need to be met.

IX. Concomitant Therapy

Patients were not enrolled in the study if they had received systemic antimicrobial therapy within 48 hours before enrollment.

Non-study antibacterial agents were not be administered during the study period, from enrollment through completion of the late follow-up visit (+28 to +42 days post-treatment) unless patients were considered treatment failures or clinical relapses.

Efforts were made to minimize the use of concomitant medications of any kind during the duration of study medication administration.

Patients requiring treatment with sucralfate or divalent and trivalent cations, such as iron, multivitamin preparations, or antacids containing magnesium, aluminum, or calcium, were instructed take such medications six or more hours before or two or more hours after the dose of study drug.

Patients on concomitant therapy with warfarin or theophylline were only included in the study if provision was made to monitor for adequate coagulation parameters and theophylline levels during the study.

All concomitant medications were recorded by the investigator.

X. Treatment Compliance

Patients were instructed to bring their study medication bottles with them to the during-therapy visit (Day 3 to 5) and TOC visit (Day +5 to +11). If a patient failed treatment or discontinued study drug therapy prematurely, unused medication was to be returned at the visit at which this occurred. In order to document patient compliance, a count of any unused study drug was recorded. Patients who had taken $\geq 80\%$ of the scheduled doses were considered to be compliant with the study protocol.

XI. Efficacy and Safety Assessments

All study procedures are summarized in the Trial Flow Chart shown in Table 1.

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TABLE 1
Trial Flow Chart

Activity	Pre-Rx ^a	During Therapy (Day 3-5)	Test-of-Cure (Day +5 to +11)	Premature D/C of Rx (if applicable)	Post-Alternative Rx (if applicable) (Day +2 to +4)	Late Follow-Up Visit (Day +28 to +42)
Evaluation of patient eligibility/medical history/health status	X					
Physical examination	X					
Brief interval physical examination/Vital signs		X	X	X	X	X
Obtained signed informed consent	X					
Pregnancy test (urine/serum) ^b	X		X	X		
Pyuria measurement	X	X	X	X		X
Clean-catch midstream urine specimen: culture, colony count, susceptibility test, urinalysis	X	X	X	X		X
Blood cultures	X	X ^c				
CBC/platelets/ blood chemistry, Theophylline/PT ^d	X	X	X	X		
Clinical assessment	X	X	X	X	X	X
Assessment of patient compliance with study medication dosing regimen		X	X	X		
Monitor Adverse Events ^e		X	X	X	X	X

^a Within 48 hours before onset of drug therapy.

^b Patients may be enrolled on the basis of a negative urine pregnancy test performed in the clinic. A serum pregnancy test also must be sent to the central laboratory.

^c If initial blood culture yield pathogen(s); blood cultures should be repeated until the results are negative.

^d Theophylline levels or PT (for warfarin) are performed only if patients are taking these medications.

^e Adverse events are reported through day +5 to +11 post-treatment. Serious adverse events and deaths will be reported through day +28 to +42 post-treatment as the investigator became aware of them.

XII. Efficacy Assessments

A. Bacteriologic Outcome

The bacteriological outcome was based on the results of urine cultures performed before the start of therapy, at the TOC visit (+5 to +11 days post-treatment), and at the late follow-up visit (+28 to +42 days post-treatment) or premature discontinuation visit (if applicable). All urine specimens were processed for culture and susceptibility testing by a central laboratory. Urine specimens for culture were obtained by the mid-stream clean-catch urine technique or by catheterization and a quantitative count was performed by the central laboratory.

Reviewer's Comment: The primary efficacy endpoint is eradication of the baseline pathogen at the TOC visit (+5 to +11 days post-treatment). All other outcomes described below (i.e., persistence, superinfection, new infection, and indeterminate) are considered failures by the applicant.

1. TOC visit (Day +5 to +11 post-treatment)

The bacteriological outcome at the TOC visit was graded as follows:

Eradication: A urine culture, obtained within the Day +5 to +11 post-treatment window, showing that all uropathogens found at study entry in a quantity of $\geq 10^5$ CFU/mL were reduced to $< 10^4$ CFU/mL.

Persistence: A urine culture, obtained any time after the completion of therapy, grew $\geq 10^4$ CFU/mL of the original uropathogen.

Superinfection: A urine culture grew $\geq 10^5$ CFU/mL of a uropathogen other than the baseline pathogen at any time during the course of active therapy.

New infection: A pathogen other than the original microorganism found at baseline at a level $\geq 10^5$ CFU/mL, was present at a level $\geq 10^5$ CFU/mL anytime after treatment was completed.

Indeterminate: It was not possible to determine bacteriological outcome. The reason for an indeterminate evaluation should be documented.

Patient outcome graded as indeterminate at this visit was invalid for efficacy evaluation.

2. Late follow-up visit (Day +28 to +42 post-treatment)

The bacteriological outcome at the late follow-up visit was graded as follows:

Continued eradication: Causative organism(s) present in numbers $< 10^4$ CFU/mL at the TOC visit and at the late follow-up visit.

Persistence: Causative organism(s) $\geq 10^4$ CFU/mL noted at the TOC visit, regardless of the results of the culture at the follow-up visit, were carried forward.

Superinfection: Growth $\geq 10^5$ CFU/mL of a uropathogen other than the baseline pathogen at any time during the course of active study drug therapy, with symptoms of infection as previously stated.

Recurrence: Causative organism(s) in numbers $< 10^4$ CFU/mL at the TOC, but reappearance of the same organism(s) $\geq 10^4$ CFU/mL before or at the Day +28 to +42 post-treatment visit.

New infection: A pathogen other than the original microorganism isolated at baseline at a level of $\geq 10^5$ CFU/mL was present at a level $\geq 10^5$ CFU/mL anytime after treatment was finished.

Indeterminate: Bacteriological outcome could not be evaluated for any reason (e.g., post-treatment culture was not obtainable). The reason for an indeterminate evaluation must have been documented.

3. Premature discontinuation

The bacteriological outcome at premature discontinuation (if applicable) was graded as follows:

Eradication: A urine culture performed before alternative antimicrobial therapy showed that all uropathogens found at study entry in a quantity $\geq 10^5$ CFU/mL were reduced to $< 10^4$ CFU/mL.

Persistence: A urine culture performed any time after premature discontinuation of therapy grew $\geq 10^4$ CFU/mL of the original uropathogen.

New infection: A pathogen other than the original microorganism isolated at baseline at a level $\geq 10^5$ CFU/mL was present at a level $\geq 10^5$ CFU/mL anytime after treatment was prematurely discontinued.

Indeterminate: It was not possible to determine bacteriological outcome. The reason for an indeterminate evaluation must have been documented.

B. Clinical Outcome

The clinical outcome was based on serial examinations of the patient to determine the effect of therapy on the signs and symptoms of the infection. All pertinent laboratory tests or procedures that reflected the course of the UTI also were assessed. Absence or reduction of pyuria, dysuria, frequency, urgency, suprapubic pain, fever ($> 38^\circ\text{C}/100.4^\circ\text{F}$ orally), chills, flank pain, nausea and/or vomiting, and CVA tenderness on examination were used to assess the clinical response. At each evaluation, each of the clinical signs and symptoms were assigned a severity score from 0 (none present) to 3 (severe).

1. During therapy visit (Day 3-5)

The clinical outcome at the during-therapy visit was graded as follows:

Clinical improvement: A sufficient reduction in the severity and/or number of signs and symptoms of infection such that the patient could continue taking study medication to completion of 7 to 14 days of therapy.

Clinical failure: An insignificant change or worsening of signs and symptoms such that study medication could not be continued or initiation of alternative antimicrobial therapy was required.

Indeterminate: It was not possible to determine clinical outcome (e.g., <3 days of study drug exposure because of premature discontinuation due to an adverse event). The reason for an indeterminate evaluation must have been documented.

2. TOC visit (Day +5 to +11 post-treatment)

The clinical outcome at the TOC visit was graded as follows:

Clinical cure: Resolution or improvement of signs and symptoms at the TOC visit such that no additional antimicrobial therapy was administered or required.

Clinical failure: No apparent response to therapy, persisting signs and symptoms of infection, reappearance of signs and symptoms at or before the TOC visit, or the use of additional antimicrobial therapy was necessary for the current infection.

Indeterminate: It was not possible to determine clinical outcome. The reason for an indeterminate evaluation must have been documented. Patient outcome graded as indeterminate at this visit was invalid for efficacy evaluation.

3. Late follow-up visit (Day +28 to +42 post-treatment)

Clinical outcome at the late follow-up visit for those patients who did not receive alternative antimicrobial therapy at the TOC visit was graded as follows:

Continued clinical cure: Continued disappearance of acute signs and symptoms of infection or continued improvement such that alternative antimicrobial therapy was not required or administered.

Failure: An outcome of failure was carried forward from the TOC visit (Day +5 to +11 post-treatment).

Relapse: Reappearance of signs and symptoms of the current infection considered to be related to an infectious (bacterial) process such that initiation of alternative antimicrobial therapy was required.

Indeterminate: It was not possible to determine clinical outcome. The reason for an indeterminate evaluation must have been documented.

4. Premature discontinuation

Clinical outcome at premature discontinuation (if applicable) was graded as follows:

Clinical cure: Resolution or improvement of signs and symptoms at the time of discontinuation such that no additional antimicrobial therapy was administered or required.

Clinical failure: No apparent response to therapy, persistence of signs and symptoms of infection, or reappearance of signs and symptoms at the time of discontinuation; or the use of additional antimicrobial therapy is necessary for the current infection.

Indeterminate: It was not possible to determine clinical outcome. Patient outcome graded as indeterminate at this visit was invalid for efficacy evaluation. The reason for an indeterminate evaluation must have been documented.

5. Post-alternative antimicrobial therapy (Day +2 to +4 post-alternative antimicrobial therapy)

The clinical outcome for those patients who received alternative antimicrobial therapy was graded as follows:

Clinical cure: Resolution or improvement of signs and symptoms at the end of alternative antimicrobial therapy such that no additional antimicrobial therapy was administered or required.

Clinical Failure: No apparent response to therapy, persistence of signs and symptoms of infection, or reappearance of signs and symptoms at or before this visit requiring alternative antimicrobial therapy for the infection.

Indeterminate: It was not possible to determine clinical outcome. The reason for an indeterminate evaluation must have been documented.

C. Safety Assessments

The safety parameters evaluated were clinical adverse events, blood chemistry and hematology, urinalysis, theophylline levels and prothrombin time (if applicable), and a pregnancy test before treatment (urine test with confirmation by a serum pregnancy test), at the TOC visit, and at the time the drug was prematurely discontinued (if applicable). Each patient was carefully monitored for adverse events, including clinical laboratory test variables.

The definition of an adverse event was any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product,

and which did not necessarily have to have a causal relationship (association) with this treatment. The adverse event may be: a new illness; worsening of a sign or symptom of the condition under treatment or of a concomitant illness; an effect of the study medication; an effect of the comparator drug; an effect related to study procedure; or a combination of 1 or more of these factors.

A laboratory test result that was abnormal or represented a clinically significant change from baseline was to be recorded as an adverse event if any of the following conditions was met: it resulted in discontinuation of treatment with study drug; there were clinical manifestations; treatment was required; or the investigator believed the event to be relevant. Each event was to be described in detail along with start and stop dates, intensity, relationship to investigational product, action taken, and outcome.

An assessment was made of the seriousness, intensity, and relationship of the adverse event to the administration of the study medication. Adverse events were reported through the TOC visit. Patients who experienced adverse events during the study were to be followed until the events either resolved or stabilized.

A complete physical examination was conducted at the pre-therapy visit. Interval physical examinations, including vital signs, were conducted at the during-therapy visit (Day 3 to 5), TOC visit (Day +5 to +11 post-treatment) and the late follow-up visit (Day +28 to +42 post-treatment) or, if applicable, the premature discontinuation visit, and the post-alternative antibiotic visit (+2 to +4 days post-treatment).

Blood and urine samples were obtained from each patient for safety purposes at the pre-therapy and TOC visits, and if applicable, the premature discontinuation visit. Specimens for laboratory testing could also be obtained during therapy if deemed necessary by the investigator. The laboratory safety variables evaluated in this study included the following:

Hematology: hemoglobin; hematocrit; white blood cell (WBC) count with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, and basophils); and platelet count; and prothrombin time (PT) and INR (only for patients receiving concomitant warfarin).

Serum chemistry: alanine transaminase (ALT/SGOT), aspartate transaminase (AST/SGPT), lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, serum creatinine, blood urea nitrogen (BUN), uric acid, amylase, gamma glutamyl transpeptidase (GGT), and serum glucose. In addition, theophylline serum concentrations for any patients receiving concomitant theophylline, and serum pregnancy test for women of childbearing potential.

Urinalysis: Semiquantitative and microscopic examination for appearance, specific gravity, leukocytes, blood/erythrocytes, nitrites, protein, pH, ketones, bilirubin, and glucose. For women of childbearing potential, a urine pregnancy test was performed at the investigative site, which was confirmed by a serum pregnancy test.

XIII. Statistical and Analytical Plan

A. Analysis Populations

1. Valid for Efficacy (i.e., Per Protocol) Population

The primary population for analysis was specified as the population of patients valid for efficacy. For a course of therapy to be judged valid for evaluating the primary efficacy parameter (i.e., bacteriological outcome at the TOC visit), the following criteria must have been met:

- A diagnosis of complicated UTI must have been confirmed before treatment on the basis of the presence of signs and symptoms consistent with a lower UTI, with underlying conditions as noted in the inclusion criteria or a diagnosis of AUP must have been confirmed on the basis of the presence of fever ($>38^{\circ}\text{C}/100.4^{\circ}\text{F}$ orally), chills, and flank pain, and a positive urine culture, with recovery of a causative organism(s) present in a quantity $\geq 10^5$ CFU/mL.
- For patients with indwelling catheters, if two or more pathogens grew from the baseline urine culture, all isolates were considered to be contaminants (i.e., unevaluable), unless the same pathogen was also isolated from a simultaneously obtained blood culture specimen. If the same pathogen grew in the urine at $\geq 10^5$ CFU/mL and was isolated from the blood, then it was considered to be an evaluable pathogen.
- All inclusion/exclusion criteria must have been met.
- The study drug must have been administered for a minimum of 3 days if the treatment result was failure or a minimum of 7 days if the treatment result was success.
- Bacteriological outcome must have been determined at the TOC visit (Day +5 to +11 post-treatment) unless the patient's outcome was early treatment failure. An indeterminate designation at the TOC visit invalidated the patient data for efficacy evaluation.
- No other systemic antibacterial agent must have been administered with the study drug or during the study period up through the TOC (Day +5 to +11 post-treatment) visit unless the patient failed treatment.
- Adequate compliance must have been documented for each patient with $\geq 80\%$ of study medication taken.
- No protocol violation may have occurred during the course of therapy influencing treatment efficacy.
- The study blind could not have been broken.

2. Valid for Safety (i.e., Intent-to-Treat) Population

Supportive analyses were performed on this population, which includes all patients who received at least one dose of medication.

Reviewer's Comment: The applicant did not specify a Modified Intent-to-Treat (MITT) population, which would include all patients with a pathogen identified at baseline who received at least one dose of study drug. The Division defined and evaluated an MITT population, in addition to the applicant's valid for efficacy (Per Protocol) population. See Results section for additional information.

B. Applicant's Proposed Efficacy Analysis

The primary efficacy objective of the study is to demonstrate non-inferiority of the Cipro XR 1000 mg once daily group to the Cipro 500 mg twice daily (BID) group. A two-sided 95% confidence interval for the weighted difference between the eradication rates for each treatment group (Cipro XR minus Cipro BID) was constructed using Mantel-Haenszel weights (weighting by infection type). Non-inferiority was defined statistically as the lower limit of the two-sided 95% confidence interval for the difference between groups being less than -10%. In addition to the Mantel-Haenszel confidence interval, supportive confidence intervals were constructed using the normal approximation to the binomial distribution, with a continuity correction.

Analysis of infection type by treatment interaction for the primary efficacy variable was planned, using either the Breslow-Day test or Zelen's test. If the interaction was significant, exploratory analyses were planned to investigate the source of the interaction.

Reviewer's Comment: Although not specified by the applicant in their protocol, if an infection type by treatment interaction at the TOC visit is seen, the Division does not consider it appropriate to pool efficacy results for cUTI and AUP patients.

For analyses performed on the valid-for-efficacy (Per Protocol) population, missing and indeterminate responses were to be excluded. For the valid-for-safety (Intent-to-Treat) population, these responses were to be included as failures.

Statistical tests also were planned for comparability of demographic data and baseline medical characteristics. Chi-square tests were planned for categorical variables, and one-way analysis of variance was planned for continuous variables.

C. Applicant's Proposed Safety Analysis

Comparisons of the incidence rates of adverse events were done in a descriptive manner. Events were to be tabulated by type (according to the COSTART glossary) and frequency for all events and for those events considered by the investigator to have a study drug relationship of possible or probable. Laboratory data were to be analyzed using descriptive statistics and identification of values outside the normal range.

XIV. Changes in the Conduct of the Study

The original protocol was amended 7 times during the study. A summary of each amendment is provided below.

Amendment 1 – March 19, 2001

The purpose of the amendment was to incorporate changes to the protocol based on suggestions from the FDA at the End of Phase II meeting. These changes included:

- Revising the number of study centers participating in the study
- Add examples of symptoms of lower urinary tract infection that may be seen with pyelonephritis
- Revising the sample size estimate based on a change in the lower limit of equivalence for the difference between treatment groups (i.e., delta) from -15 percentage points to -10 percentage points
- Clarifying the process for handling blood culture specimens
- Adding the requirement for a local lab to perform blood cultures
- Modifying the Trial Flow Chart

Amendment 2 – April 25, 2001

The purpose of the amendment was to incorporate additional changes to the protocol due to suggestions from the FDA. These revisions included:

- Modifying the language in the inclusion criteria regarding contraception use by women of childbearing potential
- Clarifying that the efficacy results would be presented descriptively by strata based on the presence or absence of pyelonephritis

Amendment 3 – July 16, 2001

The purpose of this amendment was to change the definition of Recurrence (Bacteriological outcome at the Late Follow-up Visit) from $> 10^5$ CFU/mL to $\geq 10^4$ CFU/mL before or at the +28 to +42 day post-treatment visit.

Amendment 4 – October 26, 2001

The purpose of this amendment was to remove restriction of enrollment of patients presenting with an onset of signs or symptoms of 72 hours or less prior to study entry.

Amendment 5 – December 10, 2001

The purpose of this amendment was to:

- Change the signs in the inclusion criteria for the complicated UTI patients (Stratum II) from two signs and symptoms to one sign and symptom plus an underlying complicating condition.
- Decrease the validity rate (from 75% to 50%) and the power of the study (from 90% to 85%) and increase the total number of bacteriologically valid patients enrolled (from 306 to 474). In addition, the true failure rate was reduced (17% to 15%).

Amendment 6 – April 16, 2002

The purpose of this amendment was to:

- Replace the ICD-9 Code with MedDRA code
- Clarify the classification of two or more pathogens isolated from a baseline urine culture
- Provide specific schedule for possible concomitant administration of sucralfate, divalent and trivalent cations, multivitamin preparations or antacids relative to study drug administration
- Correct the study visit window during which a systemic bacterial agent cannot be administered for a patient to be judged evaluable for efficacy analysis
- Clarify the terms "Clinical Cure" and "Clinical Failure"
- Correct the weighted difference rate
- Add INR and serum glucose to the list of safety laboratory tests
- Slightly revise the definition of an adverse event

Amendment 7 – September 12, 2002

Before the database was locked and the study blind broken the final amendment was submitted. The purpose of the amendment was to:

- Expand the Test-of-Cure visit window from 5 to 9 days to 5 to 11 days after the last dose of study drug

Reviewer's Comment: The applicant expanded the TOC visit window in order to include more data in the analyses, since they noted a number of the patient visits occurring outside the protocol-specified window. This change resulted in the inclusion of 19 additional valid-for-efficacy patients in the analysis at the TOC visit. The long-term follow-up window of +28 to +42 days after the end of therapy was not changed.

- Correct an omission (insert the words ("... stratified and then ...") in the Overall Design and Plan of Trial section of the protocol on page 21
- Correct a typographical error in the definition of "Clinical Cure" on page 40 of the protocol
- Change the definition of "Clinical Failure" at the Test-of-Cure visit and at the time study drug therapy is prematurely discontinued back to what was stated in the original protocol, which voids the change made in Amendment 6.
- Decrease the validity rate (from 50% to 39%) and decrease the total number of bacteriologically valid patients enrolled (from 474 to 404). The power of the

study was not changed (85%). In addition, the observed failure rate was reduced (15% to 12%).

XV. Clinical Reviewer's Data Validation Methods

Validation of the efficacy data was performed by obtaining the patient Case Report Forms for 10% of all randomized patients (N=113). The patients were randomly selected (blinded to treatment) and independently reviewed.

Reviewer's Comment: The reviewer determined that the trial was conducted in accordance with the draft Guidance document and as delineated in the original protocol. The reviewer's assessment of evaluability is the same as the applicant's for all patients in this sample.

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RESULTS FOR STUDY 100275

I. Investigators

One thousand forty-two (1042) patients were enrolled at 100 investigative centers. Of the 1042 patients, 521 were assigned randomly to treatment with Cipro XR 1000 mg QD and 521 were assigned randomly to Cipro 500 mg BID.

The number of randomized patients by treatment group and investigator site can be found in Table 2 in Appendix 2. The mean number of patients enrolled is 10 per site (range 1-57). Dr. Siami's site has the largest number of randomized patients at 5.5% (57/1042) of the total population. The other top enrolling sites were Dr. Young (N=47), Dr. Tomera (N=42), Dr. O'Mahony (N=42), and Dr. Wachs (N=39).

II. Patient Accountability

The reasons for premature discontinuation from the study drug are shown in Table 3. There are 119 patients in the Cipro XR group and 91 patients in the Cipro BID group who did not complete the study as planned. There is a higher rate of premature discontinuation in the Cipro XR group than in the Cipro BID group, which is due primarily to protocol violations and adverse events. The most common protocol violations resulting in discontinuation are lack of causative organisms (i.e., no pre-therapy pathogen recovered, organism recovered at $<10^5$ CFU/mL, or no urine culture specimen obtained) and presence of a resistant organism.

TABLE 3
Reasons for Premature Discontinuation of Study Drug

	Cipro XR (N=521)	Cipro BID (N=521)
Any reason (<i>P</i> value=0.03)	119 (23%)	91 (17%)
Adverse event	28 (5%)	20 (4%)
Patient non-compliance	8 (2%)	7 (1%)
Consent withdrawn	9 (2%)	11 (2%)
Insufficient therapeutic effect	7 (1%)	4 (<1%)
Patient lost to follow-up	17 (3%)	13 (2%)
Death	2* (<1%)	0 (0%)
Protocol violation	48 (9%)	36 (7%)

* An additional 2 deaths were reported (one in Cipro XR at Day +35 and one in Cipro BID at Day +97 following study drug therapy).

The distribution of patients valid for the safety and efficacy analyses and the reasons for exclusion are shown in Table 4. The proportion of patients valid for efficacy (Per Protocol) is slightly smaller in the Cipro XR group (39.5%) compared to the Cipro BID group (44%).

The Cipro XR group has a slightly lower rate (34%) of patients who have no causative organism (i.e., no pathogen recovered, organism recovered at $<10^5$ CFU/mL, or no urine culture was done) compared to the Cipro BID group (37%). The Cipro XR group also has a higher rate (15%) of patients who have no valid TOC

urine culture result (i.e., urine culture specimen was not obtained at the TOC visit, or urine culture specimen was obtained outside the TOC visit window) as compared to the Cipro BID group (9%). The proportion of invalid patients due to the reasons organism resistant to study drug and exclusion/inclusion criteria violation also is slightly higher in the Cipro XR group (4% and 2%, respectively) as compared to the Cipro BID group (3% and 1%, respectively).

Reviewer's Comment: The applicant's category "Protocol violation" includes 16 catheterized patients, all having two or more causative organisms recovered from the pre-therapy urine culture specimen without the same organism isolated from blood. Six other catheterized patients have reasons that could have classified them as a "protocol violation", but instead were classified otherwise by the applicant (five as "organism resistant to study drug" and one as "exclusion/inclusion criteria violation").

Reviewer's Comment: Table 4 is modified from the applicant's submission by the reviewer for clarity.

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TABLE 4
Patients Validity and Reasons for Exclusion from Analyses
All Randomized Patients (N=1042)

	Cipro XR (N=521)	Cipro BID (N=521)
All Randomized Patients	521	521
Patients Valid for Safety (i.e., Intent to Treat)	517 (99.2%)	518 (99.4%)
Patients Valid for Efficacy (i.e., Per Protocol)	206 (39.5%)	229 (44.0%)
Excluded from Safety (Intent to Treat) Analysis	4 (0.8%)	3 (0.6%)
Patient never received any study medication	4 (0.8%)	3 (0.6%)
Excluded from Efficacy (Per Protocol) Analysis	315 (60.5%)	292 (56.0%)
No causative organism isolated pre-treatment ^a	175 (33.6%)	194 (37.2%)
Inadequate duration of treatment	1 (0.2%)	4 (0.8%)
Concomitant antimicrobial therapy	1 (0.2%)	1 (0.2%)
Organism resistant to study drug	21 (4.0%)	15 (2.9%)
Noncompliance with study medication	5 (1.0%)	5 (1.0%)
Exclusion/inclusion criteria violation	21 (4.0%)	16 (3.1%)
Insufficient required clinical symptoms for inclusion	11 (2.1%)	9 (1.7%)
Lack of underlying condition	5 (1.0%)	2 (0.4%)
Liver disease or liver impairment	2 (0.4%)	1 (0.2%)
Pre-therapy antibiotics taken	3 (0.6%)	1 (0.2%)
Prohibited concomitant medication	0 (0%)	3 (0.6%)
Patient never received any study medication	4 (0.8%)	3 ^b (0.6%)
Post-therapy antibiotics taken	2 (0.4%)	2 (0.4%)
Protocol violation	9 (1.7%)	7 (1.3%)
No valid TOC urine culture ^c	76 (14.6%)	45 (8.6%)

^a no pre-therapy pathogen recovered, organism <10⁵ CFU/mL, or no urine culture specimen obtained

^b antacids or multivitamin preparations taken in violation of the protocol within 6 hours before or less than 2 hours after the dose of study drug

^c urine culture specimen was not obtained at the TOC visit, or urine culture specimen was obtained outside the TOC visit window (5 to 11 days post-treatment)

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Reviewer's Comment: Table 4A presents the number of patients valid for analyses in each of the Division's three populations, including the MITT.

TABLE 4A
Patients Valid for Analyses
All Randomized Patients (N=1042)

	Cipro XR	Cipro BID
All Randomized Patients	521	521
Patients Valid for Safety (i.e., Intent to Treat)*	517 (99.2%)	518 (99.4%)
Patients Valid for MITT (i.e., modified Intent to Treat)**	342 (65.6%)	324 (62.2%)
Patients Valid for Efficacy (i.e., Per Protocol)***	206 (39.5%)	229 (44.0%)

* Four (4) patients in the Cipro XR group and 3 patients in the Cipro BID were excluded because they never received any study medication.

** 175 patients in the Cipro XR group and 194 patients in the Cipro BID were excluded due to no pathogen identified at baseline.

***Three hundred and fifteen (315) patients in the Cipro XR group and 292 patients in the Cipro BID group were excluded for various reasons (see Table 4 above).

Reviewer's Comment: On June 18, 2003 the applicant was asked to provide additional information regarding the reasons patients were classified as "No Valid TOC urine culture" (see Table 4) by providing a tabulation of the number of patients with each specific cause for not conducting the TOC urine culture (e.g., discontinuation due to adverse event, death, lab error, etc.).

On June 27, 2003 the applicant submitted Table 4B shown below. The reviewer investigated all individual patients excluded by the applicant in the PP population due to "protocol violations" within the "No TOC urine culture" category and determined that patients were not always categorized by the major reason for exclusion. For example, a patient in the category "No valid TOC urine culture" may have been excluded due to a ciprofloxacin resistant pathogen, and yet there is also an exclusion category called "Organism Resistant to Study Drug" (see Table 4).

As a result, the reviewer sent a request to the applicant in a fax on July 17, 2003, asking the applicant to reclassify patients based upon the root cause for exclusion from the PP population. The applicant was asked to avoid categories of "protocol violation" and "no valid TOC urine culture", as they are too non-specific.

On July 29, 2003 the applicant submitted the revised data. Upon review, the reviewer noted the reasons for exclusion of individual patients (provided by the applicant) within the new exclusion categories of "no TOC visit", "lost to follow-up", and "TOC outside the 5-11 day window", did not always match the title of the exclusion category. For example, patients 50012 and 15004 were classified as "no TOC visit" and yet the comments from the patient's CRFs indicated that these patients had ciprofloxacin resistant organisms.

The reviewer accepts the applicant's revised classification of reasons for exclusion of patients from the PP population, despite the inconsistencies noted above because they are not believed to have a significant impact on the overall results. Table 4 was

recreated by the reviewer, using the revised data submitted by the applicant on July 29, 2003, and the results can be seen in Table 5.

TABLE 4B
Patients Invalid in the Per Protocol (or Valid for Efficacy) Population
Due to No TOC Urine Culture

	Cipro XR	Cipro BID
Invalid due to No TOC Urine Culture	76 (15%)	45 (9%)
Premature Discontinuation due to: Any Reason	44 (8%)	25 (5%)
Adverse Event	14	6
Noncompliance with Drug	0	1
Consent Withdrawn	3	5
Insufficient Therapeutic Effect	1	1
Lost to Follow-up	8	4
Death	2	0
Protocol Violation	16	8
Completed Therapy, but No TOC Urine Culture	11 (2%)	7 (1%)
TOC Culture Outside 5-11 Day Post-Treatment Window	21 (4%)	12 (2%)
Before Day 5	12	4
After Day 11	9	8
Lost to Follow-up, no discontinuation reason given	0	1

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TABLE 5
Patients Validity and Reasons for Exclusion from Analyses
All Randomized Patients (N=1042)
Revised by Applicant

	Cipro XR (N=521)	Cipro BID (N=521)
All Randomized Patients	521	521
Patients Valid for Safety (i.e., Intent to Treat)	517 (99.2%)	518 (99.4%)
Patients Valid for Efficacy (i.e., Per Protocol)	206 (39.5%)	229 (44.0%)
Excluded from Safety (Intent to Treat) Analysis	4 (0.8%)	3 (0.6%)
Patient never received any study medication	4 (0.8%)	3 (0.6%)
Excluded from Efficacy (Per Protocol) Analysis	315 (60.5%)	292 (56.0%)
No causative organism (isolated pre-treatment)	175 (33.6%)	194 (37.2%)
Concomitant or post-therapy antimicrobial	3 (0.6%)	3 (0.6%)
Organism resistant to ciprofloxacin	31 (6.0%)	18 (3.4%)
Noncompliance with study medication	5 (1.0%)	6 (1.2%)
Inclusion criteria violation	21 (4.0%)	16 (3.1%)
Patient never received any study medication	4 (0.8%)	3 (0.6%)
More than two causative organisms identified for catheterized patients	9 (1.7%)	7 (1.3%)
Premature discontinuation due to adverse event(s)	15 (2.9%)	9 (1.7%)
Lost to follow-up	8 (1.5%)	4 (0.8%)
Death	2 (0.4%)	0
Consent withdrawn	3 (0.6%)	5 (1.0%)
Insufficient therapeutic effect	1 (0.2%)	1 (0.2%)
Pre-therapy lab value violation	6 (1.2%)	6 (1.2%)
TOC culture outside 5-11 day window	21 (4.0%)	12 (2.3%)
No TOC visit	11 (2.1%)	8 (1.5%)

Reviewer's Comment: Exclusions from the PP population are greater in the Cipro XR group compared to the Cipro BID group and a differential rate in exclusion may bias the results of any analysis using this population. Therefore, the Division analyzed the results for the Modified Intent-to-Treat (MITT) population, in addition to the PP population. In the MITT population (all patients with a pathogen identified at baseline), missing and indeterminate results are included as failures.

III. Patient Groups

A. Demographic Characteristics

Demographic and other important baseline characteristics for the population of patients valid for efficacy are presented in Table 6.

The mean age (\pm standard deviation) of patients valid for efficacy is 60.1 (\pm 19.1) years in the Cipro XR treatment group and 61.2 (\pm 19.4) years in the Cipro BID group. The minimum age in both treatment groups is 18 years, and the maximum age is 96 years and 92 years in the Cipro XR and Cipro BID groups, respectively. There are more female than male patients in both treatment groups (57% in the Cipro XR group and 55% in the Cipro BID group). Most of the patients are Caucasian (82% in the Cipro XR group and 77% in the Cipro BID group). Among patients who are not Caucasian, most are categorized as Black or Hispanic (18% and 22% in the two treatment groups, respectively). Less than 1% of patients in each treatment group are Asian.

There are no statistically significant differences in demographic or baseline characteristics between treatment groups, and in general, the distribution of demographic variables is similar in the two groups. When demographic and baseline characteristics are examined by diagnosis group, the characteristics are also similar. These results are consistent with those observed for the population of patients valid for safety (data not shown).

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TABLE 6
Key Demographic and Infection Characteristics
Patients Valid for Efficacy

	Cipro XR (N=206)	Cipro BID (N=229)
Age at enrollment (years), mean	60.1	61.2
Sex, % female	57%	55%
Race, % Caucasian	82%	77%
Weight at enrollment (kg), mean	75.8	77.9
Body mass index, mean	26.6	27.4
Health status before study entry, %		
Excellent	30%	19%
Good	51%	59%
Fair	18%	21%
Poor	<1%	<1%
Duration of infection (days) mean ± SD, range	4.7 ± 9.1 (1 to 121)	4.4 ± 4.7 (1 to 34)
Infection type, % cUTI	81%	77%
Number of underlying conditions for cUTI, % ^a		
1	72%	79%
2	25%	19%
>2	3%	2%

^a Denominator is number of patients with cUTI (n=166 for Cipro XR; n=177 for Cipro BID)

Reviewer's Comment: In order to characterize the demographics of cUTI compared to AUP patients, the reviewer analyzed the age and gender of patients in both subgroups. The number of underlying conditions could not be compared between the groups, since the presence of underlying conditions was not required for AUP patients. As shown in Table 6A, patients with AUP are more likely to be young and female, compared to the cUTI patients.

TABLE 6A
Demographic Characteristics for AUP and cUTI Patients
Patients Valid for Efficacy

	AUP Patients		cUTI Patients	
	Cipro XR N=40	Cipro BID N=52	Cipro XR N=166	Cipro BID N=177
Mean age at enrollment	41 years	40 years	64 years	67 years
Number Female	33	43	85	84
Number Male	7	9	81	93

B. Bacteriology

Overall, patients with at least one causative organism comprised 342 valid for efficacy patients in the Cipro XR group (66.1%) and 324 (62.5%) patients in the Cipro BID group. The most common organisms (≥ 10 in either treatment arm)

isolated from the urine are summarized by diagnosis and treatment group in the valid for efficacy population in Table 7. Some patients have more than one organism isolated at enrollment. The Cipro XR group has slightly fewer valid for efficacy patients with causative organisms in the urine regardless of infection type; however, the numbers of patients with each common causative organism are similar in the two treatment groups.

TABLE 7
Most Common (≥ 10 organisms per Treatment Group) Causative Organisms
in Urine at Enrollment
Patients Valid for Efficacy ^a

	Cipro XR	Cipro BID
AUP patients with at least 1 organism	40	52
<i>Escherichia coli</i>	36	41
cUTI patients with at least 1 organism	166	177
<i>Escherichia coli</i>	94	92
<i>Klebsiella pneumoniae</i>	23	23
<i>Enterococcus faecalis</i>	18	21
<i>Proteus mirabilis</i>	12	11

^a A patient could have more than one organism

Escherichia coli was isolated from the pre-treatment (enrollment) blood culture specimen of 9 AUP patients (5 in the Cipro XR group and 4 in the Cipro BID group). *E. coli* was the only causative organism recovered from the blood of patients with cUTI (one in each treatment group).

These results are consistent with those observed for the population of patients valid for safety. Patients with at least one causative organism comprised 327 valid for safety patients in the Cipro XR group (63%) and 315 (61%) patients in the Cipro BID group. Among patients who had a causative organism in the urine, 207 are non-evaluable in the efficacy analysis due primarily to no TOC culture (n=121), exclusion/inclusion criteria violation (n=35), or isolation of ciprofloxacin-resistant organisms at pre-therapy (n=31).

Eight (8) patients in the valid for safety population received antimicrobial agents before the start of study drug therapy (6 in the Cipro XR group and 2 in Cipro BID group). Five different antimicrobial drugs were used (ciprofloxacin [ophthalmic and systemic], ofloxacin, methenamine, nitrofurantoin, and metronidazole).

C. Concomitant Medications

The incidence rate of concomitant medication use (i.e., medications started after randomization) in the valid for safety population is 23% in the Cipro XR group and 24% in the Cipro BID group. The most commonly used treatment-emergent medications are in the nervous system class (12% in the Cipro XR group and 13% in the Cipro BID group) for reasons including flank pain, headache, back pain, fever, anesthesia, etc. The rates of use of concomitant medications by medication class are consistent in the two treatment groups.

In the valid for safety population, 38 patients in the Cipro XR group and 16 patients in the Cipro BID group received concomitant antimicrobials. Antimicrobial agents used more frequently include trimethoprim/sulfamethoxazole (4 and 0 patients in the Cipro XR and Cipro BID groups, respectively), ceftriaxone (3 and 2, respectively), and nitrofurantion (6 and 2, respectively).

D. Signs and Symptoms of Disease

All valid for efficacy patients with AUP reported the presence of chills, flank pain, and fever as specified in the protocol. In 77% of patients, flank pain is rated as moderate or severe. The most common additional signs and symptoms in valid patients with pyelonephritis are backache (92%), urgency (91%), frequency (90%), and malaise (85%). Vomiting (33%) and hematuria (46%) are the only symptoms present in less than 80% of the AUP patients.

Frequency is the most common symptom in the complicated UTI patients (87% of valid cUTI patients had this symptom). The two treatment groups are well balanced with respect to the distribution of signs/symptoms and their severity in both diagnosis groups (i.e., AUP and cUTI).

E. Underlying Conditions (cUTI group)

The percentage of valid for efficacy patients with cUTI who have more than one valid underlying condition is higher in the Cipro XR (28%) than the Cipro BID (21%) group as shown in Table 6 above. Table 8 presents a summary of the distribution of underlying conditions at study entry. The underlying conditions reported include the five specified in the protocol (i.e., 100 mL residual urine after voiding; urinary retention due to benign prostatic hypertrophy; indwelling urinary catheter; neurogenic bladder; and obstructive uropathy due to nephrolithiasis, tumor, or fibrosis) plus additional underlying conditions (i.e., bladder cancer, other anatomical abnormalities, obstructive uropathy due to other etiology, and cystocele or cystourethrocele).

Reviewer's Comment: According to the applicant's statistical plan, patients with indwelling catheters that grew two or more pathogens from the baseline urine culture were to be considered unevaluable in the efficacy population, unless the same pathogen was also isolated from a simultaneously obtained blood culture specimen. If the same pathogen grew in the urine at $\geq 10^5$ CFU/mL and was isolated from the blood, then the patient would be considered to be evaluable. None of the 21 patients with indwelling catheters grew two or more pathogens from the baseline blood culture. There are 20 patients (9 Cipro XR and 11 Cipro BID patients) without indwelling catheters in the valid for efficacy population who grew multiple pathogens.

The combination of underlying conditions is shown in Table 8. Patients are reported according to one underlying condition alone or a specific underlying condition plus other underlying conditions. The two treatment groups are similar with respect to the distribution of type of underlying condition(s).

Reviewer's Comment: Table 8 is modified from the applicant's submission by the reviewer for clarity.

TABLE 8
Underlying Conditions for cUTI Patients at Study Entry
cUTI Patients Valid for Efficacy

	Number (%)	
	Cipro XR (N=166)	Cipro BID (N=177)
100 mL Residual Urine after Voiding	64 (39)	71 (40)
<i>alone</i>	37 (22)	41 (23)
<i>plus other condition</i>	27 (16)	30 (17)
Benign Prostatic Hypertrophy with Urinary Retention	35 (21)	34 (19)
<i>alone</i>	12 (7)	20 (11)
<i>plus other condition</i>	23 (14)	14 (8)
Indwelling Urinary Catheter	12 (7)	9 (5)
<i>alone</i>	2 (1)	2 (1)
<i>plus other condition</i>	10 (6)	7 (4)
Neurogenic Bladder	51 (31)	61 (34)
<i>alone</i>	34 (20)	45 (25)
<i>plus other condition</i>	17 (10)	16 (9)
Obstructive Uropathy due to Nephrolithiasis, Tumor, or Fibrosis	49 (40)	38 (21)
<i>alone</i>	34 (20)	28 (16)
<i>plus other condition</i>	15 (9)	10 (6)
Bladder Cancer	1 (1)	0 (0)
<i>alone</i>	0 (0)	
<i>plus other condition</i>	1 (1)	
Other Anatomical Abnormalities/Obstructive Uropathy Due to Other Etiology	4 (2)	5 (3)
<i>alone</i>	0 (0)	4 (2)
<i>plus other condition</i>	4 (2)	1 (1)
Cystocele/Cystourethrocele	5 (3)	1 (1)
<i>alone</i>	0 (0)	0 (0)
<i>plus other condition</i>	5 (3)	1 (1)

F. Adjunct Therapeutics/Procedures

In the valid for safety population, 51 (10%) patients in the Cipro XR group and 37 (7%) patients in the Cipro BID group required a therapeutic adjunct or diagnostic/surgical procedure. The most frequently identified therapeutic adjuncts are the administration of intravenous fluids (17 Cipro XR patients vs. 14 Cipro BID patients) and the use of a urinary catheter (e.g., indwelling [16 Cipro XR patients vs. 10 Cipro BID patients] and intermittent [10 Cipro XR patients vs. 6 Cipro BID patients]). The proportion of patients using each adjunct is similar between groups.

IV. Compliance Results

The number of tablets taken is summarized in Table 9 for all patients valid for efficacy and safety. All of these patients received treatment over a course of 5 to 15 days, with a mean (\pm SD) of 12 ± 3 days in both groups.

Reviewer's Comment: Table 9 is modified from the applicant's submission by the reviewer for clarity.

TABLE 9
Medication Compliance by Number of Tablets Taken

Number of Tablets Missing (Presumed Taken)	Number of Patients (% of Total Population)			
	Valid for Efficacy		Valid for Safety	
	Cipro XR (N=206)	Cipro BID (N=229)	Cipro XR (N=517)	Cipro BID (N=518)
< 6	0 (0)	0 (0)	27 (5)	14 (3)
> 6 to 18	0 (0)	4 (2)	48 (9)	41 (8)
> 18 to 30	81 (39)	84 (37)	171 (33)	170 (33)
> 30 to 42	119 (58)	137 (60)	248 (48)	273 (53)
Missing Data	6 (3)	4 (2)	23 (4)	20 (4)

Of note, during the conduct of the study, a short-fill in Bottle #2 was discovered for patient numbers 601 through 900. The short-fill resulted in 23 placebo tablets placed in Bottle #2 instead of 28 placebo tablets. On October 31, 2001, the applicant became aware of the situation and on November 1, 2001 notified all sites and instructed them not to dispense medication bottles with numbers 601 through 900. Sixteen patients were affected by the short-fill and all were in the Cipro XR group. Of these, 8 are considered valid for efficacy and safety and all 8 received at least 7 days of study medication. One of the 8 patients (98001) had 11 days of therapy and had a persistence at the TOC. The remaining 8 patients are valid for safety only.

V. Efficacy Results for the Valid for Efficacy Population – Bacteriologic Response

A. Eradication at the TOC Visit

The bacteriological eradication rate at the TOC visit in patients valid for efficacy, the primary efficacy variable, is shown in Table 10. Overall eradication in cUTI and AUP patients combined is 88.8% in the Cipro XR group and 85.2% in the Cipro BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (-2.4%, 10.3%) is above -10%, indicating the non-inferiority of Cipro XR 1000 mg QD compared to Cipro 500 mg BID.

Reviewer's Comment: In addition to the Mantel-Haenszel confidence interval, the applicant calculated supportive confidence intervals using the normal approximation to the binomial distribution, with a continuity correction. For the difference in bacteriological eradication rates at the TOC visit in patients valid for efficacy, the 95% confidence interval using the normal approximation to the binomial distribution with continuity correction is (-3.1%, 10.4%).

TABLE 10
Number of Patients (%) with Bacteriological Response
at the TOC Visit (+5 to +11 Days)
Patients Valid for Efficacy

	Cipro XR	Cipro BID
<i>All Patients</i>	(N=206)	(N=229)
Eradication	183 (88.8%)	195 (85.2%)
Persistence	10 (4.9%)	17 (7.4%)
Superinfection	5 (2.4%)	3 (1.3%)
New infection	8 (3.9%)	14 (6.1%)
Eradication Rate^a	183/206 (88.8%)	195/229 (85.2%)
<i>AUP Patients</i>	(n=40)	(n=52)
Eradication	35 (87.5%)	51 (98.1%)
Persistence	2 (5.0%)	1 (1.9%)
New infection	3 (7.5%)	0
<i>cUTI Patients</i>	(n=166)	(n=177)
Eradication	148 (89.2%)	144 (81.4%)
Persistence	8 (4.8%)	16 (9.0%)
Superinfection	5 (3.0%)	3 (1.7%)
New infection	5 (3.0%)	14 (7.9%)

^a Eradication rate for all patients (cUTI plus AUP); 95% Confidence Interval: (-2.4%, 10.3%)

The *P* value from the Breslow-Day test for treatment-by-infection interaction is significant at 0.008, indicating that the treatment effect is different between AUP patients and cUTI patients.

Reviewer's Comment: Since there is a treatment-by-infection interaction, the Division does not consider it appropriate to pool results for patients with AUP and cUTI. Therefore the clinical and statistical reviewers evaluated AUP and cUTI patients separately.

The eradication rates for the AUP patients are higher in the Cipro BID group (98.1%) than in the Cipro XR group (87.5%) [corresponding 97.5% confidence interval of the difference (-34.8%, 6.2%)]. In contrast the eradication rates for cUTI patients are higher in the Cipro XR group (89.2%) than in the Cipro BID group (81.4%) [corresponding 97.5% confidence interval of the difference* (-0.7, 16.3%)].*

**When calculating the results of each stratum alone an adjustment must be made for multiple comparisons (i.e., use of 97.5% confidence intervals for the differences between Cipro XR and Cipro BID within the AUP and cUTI subgroups).*

For AUP patients, the 97.5% confidence interval for the treatment difference in bacteriologic eradication rates is below -10%, indicating the conditions for non-inferiority of Cipro XR compared to Cipro BID were not met. For cUTI patients, the 97.5% confidence interval of difference is above -10% (and almost above

zero), indicating non-inferiority of Cipro XR compared to Cipro BID (and a trend toward superiority).

Additional analyses were performed in an attempt to assess how Cipro XR compares to Cipro BID with respect to persistence of the baseline pathogen and subsequent clinical response. See the following sections on AUP and cUTI patients.

1. AUP Patients

When comparing all patients with a diagnosis of AUP, the two treatment arms are well balanced with respect to demographics, baseline characteristics, and severity of signs and symptoms at study entry (data not shown).

Of the 40 patients with AUP treated with Cipro XR, 35 were eradicated (32 *E. coli*, 1 *P. aeruginosa*, 2 *K. pneumoniae*), 2 had persistence (1 *E. coli* and 1 *E. faecalis*), and 3 developed new infections with *E. faecalis* (2 with *E. coli* as baseline pathogen and one with *S. aprophyticus*).

Of the 52 patients with AUP treated with Cipro BID, 51 were eradicated (40 *E. coli*, 2 *P. mirabilis*, 3 *E. faecalis*, 2 *K. pneumoniae*, 1 each with *C. koseri*, *S. aureus*, *S. saprophyticus*, *W. virosa*; and one with *E. coli* and *P. mirabilis*, one with *E. coli* and *E. faecalis*, and one *E. faecalis* and *C. koseri*). One patient had persistence of *E. faecalis*.

In the AUP patients treated with Cipro XR, three developed a new infection as compared to none in the Cipro BID group, as shown in Table 11. A short narrative of each patient's clinical course follows the table.

Two of the 3 patients had *E. coli* isolated as the causative organism at the pre-therapy visit and developed *E. faecalis* in a quantity of $\geq 10^5$ CFU/mL at the TOC visit. Neither had any clinical signs or symptoms of infection at the TOC or late follow-up visits, and no alternative antibiotics were deemed necessary by the investigator.

Reviewer's Comment: The emergence of Enterococcus species as a new pathogen at the TOC visit in three patients in the Cipro XR arm is notable. In order to better understand the effect of ciprofloxacin on Enterococcus, the reviewer identified all AUP patients with Enterococcus species isolated at baseline or the TOC visit. There are 10 patients with AUP (4 in the Cipro XR group and 6 in the Cipro BID group) that had an Enterococcus species isolated at baseline or the TOC visit. Of the 4 Cipro XR patients, three had new infections with Enterococcus sp. at the TOC visit (see Table 10 above) and the fourth had persistence of Enterococcus faecalis from baseline (patient 0209039). No patient in the Cipro XR arm had Enterococcus isolated at baseline. Of the 6 Cipro BID patients, five had Enterococcus faecalis isolated at baseline and were eradicated of at the TOC visit (patients 148024, 029042, 082040, 148019, 148027) and the sixth had persistence of Enterococcus faecalis from baseline (patient 013017). No patient in the Cipro BID arm developed a new infection due to Enterococcus at the TOC visit.

Reviewer's Comment: Table 11 has been modified from the applicant's table by the reviewer for clarity.

TABLE 11
Cipro XR Patients with AUP who Experienced a New Infection at the TOC Visit

Patient No.	Age (yr)/Sex	Duration of Treatment (d)	Urine Pathogen(s)	MIC (µg/mL)	Bacteriological Response at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
62019	21/F	10	<i>E. coli</i> (pre-therapy)	0.015	Eradication (Continued eradication)	Cure (Continued cure)	No
			<i>E. faecalis</i> (TOC)	1.00	New Infection (Eradication)		
82039	19/F	8	<i>E. coli</i> (pre-therapy)	0.015	Eradication (Continued eradication)	Cure (Continued cure)	No
			<i>E. faecalis</i> (TOC)	0.5	New Infection (Eradication)		
			<i>E. faecium</i> (TOC)	16	New Infection (Eradication)		
148023	18/F	11	<i>S. saprophyticus</i> ^a (pre-therapy)	0.120	Eradication (Indeterminate)	Cure (Cure ^b)	Yes ^c
			<i>E. faecalis</i> (TOC)	1.00	New Infection (Indeterminate)		

^a Pre-therapy urine culture also contained 65,000 CFU/mL of *E. coli* (MIC 0.015 µg/mL)

^b Post-alternative therapy visit

^c Ciprofloxacin 500 mg BID for 7 days following the completion of study drug

Patient Narratives

Patient 62019 is a 21-year-old female with a medical history significant for a urinary tract infection in 1999. She was not receiving any concomitant medications. The patient presented with 4 days of signs and symptoms of pyelonephritis. In general, her clinical presentation comprised mild/moderate signs

and symptoms except for severe dysuria and back pain. Her temperature at study entry was 38.3° C (orally), and the white blood cell (WBC) count was 9.7×10^9 /L. Her pretherapy urine culture result was positive for *E. coli*, and she was assigned randomly to treatment with Cipro XR 1000 mg QD, which she received for 10 days. At the TOC visit, the patient's response was evaluated as clinical cure. She was afebrile, and her WBC count had decreased to 6.8×10^9 /L. A repeat urine culture result at the TOC visit was negative for *E. coli* (eradication); however, *E. faecalis* was identified in a quantity of $\geq 10^5$ CFU/mL (new infection). No alternative antibiotics were given. At follow-up, the patient remained afebrile and her response was evaluated as continued clinical cure. Urine culture results revealed continued eradication of *E. coli* and absence of *E. faecalis*.

Patient 82039 is a 19-year-old female with no significant medical history. Concomitant medications included acetaminophen and an oral contraceptive agent. The patient presented with 3 days of signs and symptoms of pyelonephritis, a temperature of 38.3° C (orally), and a WBC count of 11.6×10^9 /L. Her pretherapy urine culture result was positive for *E. coli*, and she was assigned randomly to treatment with Cipro XR 1000 mg QD, which she received for 8 days. At the TOC visit, the patient's response was evaluated as clinical cure (no remaining signs or symptoms of infection). The WBC count had decreased to 6.4×10^9 /L. A repeat urine culture result obtained at the TOC visit was negative for *E. coli* (eradication); however, *E. faecalis* and *E. faecium* both were identified in a quantity

$\geq 10^5$ CFU/mL (new infection). No alternative antibiotics were given. At follow-up, the patient's response was assessed as continued clinical cure. Urine culture results at follow-up revealed continued eradication of *E. coli* and absence of both *Enterococcus* species.

Patient 148023 is an 18-year-old female with no significant medical history, and she was not receiving any concomitant medications. The patient presented with 2 days of signs and symptoms of pyelonephritis. In general, her clinical presentation comprised mild/moderate signs and symptoms, a temperature of 38.8° C (orally), and a WBC count of 9.7×10^9 /L. Her pretherapy urine culture result was positive for *S. saprophyticus*, and she was assigned randomly to treatment with Cipro XR 1000 mg QD, which she received for 11 days. At the TOC visit, the patient's response was evaluated as clinical cure. She was afebrile, and her WBC count had decreased to 5.5×10^9 /L. A repeat urine culture result at the TOC visit was negative for *S. saprophyticus* (eradication); however, *E. faecalis* was identified in a quantity of $\geq 10^5$ CFU/mL (new infection). Alternative antibiotic therapy was prescribed (ciprofloxacin 500 mg BID for 7 days) 18 days following the completion of study drug therapy. At the post-alternative therapy visit the patient's clinical response was evaluated as clinical cure; there was no follow-up bacteriological evaluation.

2. cUTI Patients

As previously mentioned, among patients with cUTI, the bacteriologic eradication rates at the TOC visit are higher in the Cipro XR group (148/166, 89.2%) compared to the Cipro BID group (144/177, 81.4%). The 97.5% confidence interval of the difference is [-0.7, 16.3%].

Of the 166 patients with cUTI treated with Cipro XR, 148 were eradicated, 8 have persistence with the following organisms: *E. coli* (3), *S. aureus* (2), and *K. pneumoniae*, *P. mirabilis*, and *C. freundii* (one each). Five patients developed superinfections with *S. aureus* (3) and *P. aeruginosa* (2) and five developed new infections with *E. faecalis* (3), and *S. aureus* and *P. stuartii* (one each).

Of the 177 patients with cUTI treated with Cipro BID, 144 were eradicated, 16 have persistence with the following organisms: *E. faecalis* (7), *K. pneumoniae* (4), *E. coli* (2), and *S. aureus*, *K. oxytoca*, and 1 *C. koseri* (one each). Three patients developed superinfections (one each of *E. faecalis*, *K. pneumoniae*, and *A. faecalis*) and fourteen developed new infections (*E. faecalis* (6), *S. aureus* (4), *E. coli*, *P. mirabilis*, *A. calcoaceticus*, *C. freundii*, and *Enterococcus* sp. (one each).

The number of patients with persistent organisms and new infections is disproportionately lower in the Cipro XR group (8 and 5, respectively) compared to the Cipro BID group (16 and 14, respectively). The organisms persisting in each treatment group are as shown in Table 12.

Reviewer's Comment: Table 12 was created by the reviewer.

TABLE 12
Organisms Persisting at TOC (+5 to +11 Days) in cUTI Patients
Patients Valid for Efficacy

	Cipro XR	Cipro BID
<i>E. faecalis</i>	0	7
<i>E. coli</i>	3	2
<i>K. pneumoniae</i>	1	4
<i>S. aureus</i>	2	1
<i>P. mirabilis</i>	1	0
<i>C. freundii</i>	1	0
<i>K. oxytoca</i>	0	1
<i>C. koseri</i>	0	1

Organisms causing new infections, or superinfections, will be discussed subsequently.

3. By Organism

The most commonly isolated organisms (≥ 10 in either treatment group) recovered from the urinary tract at the TOC visit are shown in Table 13. The eradication rates are high and similar between the groups, with the exception of *E. faecalis* in cUTI patients in the Cipro BID group.

TABLE 13
Bacteriological Eradication* at TOC Visit (+5 to +11 Days)
For the Most Common Organisms (≥ 10 in Either Treatment Group)
Patients Valid for Efficacy

	n/N (%)	
	Cipro XR	Cipro BID
AUP Patients		
<i>Escherichia coli</i>	35/36 (97%)	41/41 (100%)
cUTI Patients		
<i>Escherichia coli</i>	91/94 (97%)	90/92 (98%)
<i>Klebsiella pneumoniae</i>	20/21 (95%)	19/23 (83%)
<i>Enterococcus faecalis</i>	17/17 (100%)	14/21 (67%)
<i>Proteus mirabilis</i>	11/12 (92%)	10/10 (100%)

* n/N = patients with specified baseline pathogen eradicated/patients with specified baseline pathogen

The minimum inhibitory concentrations at which 90% of organisms are inhibited (MIC₉₀) for the most common causative pathogens in Table 13 above are as follows: *E. coli* (0.06 µg/mL); *K. pneumoniae* (0.5 µg/mL); *E. faecalis* (2.0 µg/mL); and *P. mirabilis* (2.0 µg/mL).

Reviewer's Comment: Additional tables showing by-organism results from the Microbiologist's review can be found in Appendix 2:

Table 14 shows the microbiological results by pathogen at the TOC visit. The eradication rates were consistent in the two treatment groups. Cipro XR had a better eradication rate against *Enterococcus faecalis* than did Cipro BID. Eradication rates for *E. coli*, by far the most common organism, were high for both treatment groups. There were very few isolates of *Enterobacter aerogenes* or *Pseudomonas aeruginosa*.

Tables 15 and 16 show the bacteriological response for AUP and cUTI patients, respectively, by MIC value of the organism. Persistence was not associated with elevated MICs for any organism.

Tables 17 and 18 show the patients valid for efficacy that had bacteriologic persistence or were clinical failures at the TOC and follow-up visits. More bacteriologic persistence and clinical failures were seen in the Cipro BID group (n = 26) compared with the Cipro XR group (n = 15).

Table 19 shows isolates with an MIC post-therapy that was more than one dilution greater than the pre-therapy MIC. Of 65 isolates from either the Cipro XR or Cipro BID groups, eleven isolates had elevated MICs at the TOC visit. The six isolates that were in the Cipro XR group included *Escherichia coli* (n = 4), *Klebsiella pneumoniae* (n = 1), and *Staphylococcus aureus* (n = 1). The MICs of two isolates of *Escherichia coli* increased to 16 µg/mL; however, the organisms were eradicated at the TOC visit, but recurred at the follow-up visit. The MIC of one isolate of *E. coli* increased from 0.015 to 0.12 µg/mL and was not eradicated and the MIC of the other isolate, which recurred at the follow-up visit, increased from 0.03 to 0.5 µg/mL. The MIC of the isolate of *K. pneumoniae* increased from 0.06 to 0.5 µg/mL, while the MIC of the isolate of *S. aureus* increased from 2 to 16 µg/mL. Neither organism was eradicated. Similar results were seen in the Cipro BID group.

a) AUP Patients

All causative pathogens and the outcome in AUP patients in the Cipro XR and Cipro BID groups are shown in Tables 20 and 21 respectively.

Reviewer's Comment: Tables 20 and 21 were created by the reviewer.

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On Original

TABLE 20
Bacteriological Eradication at TOC Visit (+5 to +11 Days)
AUP Patients treated with Cipro XR
Patients Valid for Efficacy (N=40) ^a

Urine Pathogens at Baseline	Eradication	New Infection	Persistence	Bacteriologic Eradication*
<i>E. coli</i> (N=36) ^a	33	2 (<i>E. faecalis</i>)	1	35/36 (97.2%)
<i>E. faecalis</i> (N=1)	–	–	1	0/1
<i>K. pneumoniae</i> (N=2) ^a	2	–	–	2/2 (100%)
<i>P. aeruginosa</i> (N=1)	1	–	–	1/1 (100%)
<i>S. saprophyticus</i> (N=1)	–	1 (<i>E. faecalis</i>)	–	1/1 (100%)

^a One patient had *E. coli* and *K. pneumoniae* isolated at baseline (both were eradicated)

* n/N patients with specified baseline pathogen eradicated/patients with specified baseline pathogen

TABLE 21
Bacteriological Eradication* at TOC Visit (+5 to +11 Days)
AUP Patients treated with Cipro BID
Patients Valid for Efficacy (N=52) ^{a, b, c}

Urine Pathogens at Baseline	Eradication	New Infection	Persistence	Bacteriologic Eradication*
<i>E. coli</i> (N=41) ^{a, b}	41	–	–	41/41 (100%)
<i>P. mirabilis</i> (N=3) ^a	3	–	–	3/3 (100%)
<i>E. faecalis</i> (N=5) ^{b, c}	4	–	–	4/5 (80%)
<i>K. pneumoniae</i> (N=2)	2	–	–	2/2 (100%)
<i>Citrobacter koseri</i> (N=1) ^c	1	–	–	1/1 (100%)
<i>S. aureus</i> (N=1)	1	–	–	1/1 (100%)
<i>S. saprophyticus</i> (N=1)	1	–	–	1/1 (100%)
<i>Weeksella virosa</i> (N=1)	1	–	–	1/1 (100%)

* n/N patients with specified baseline pathogen eradicated/patients with specified baseline pathogen

^a One patient had *E. coli* and *P. mirabilis* isolated at baseline (both were eradicated)

^b One patient had *E. coli* and *E. faecalis* isolated at baseline (both were eradicated)

^c One patient had *E. faecalis* and *C. koseri* isolated at baseline (both were eradicated)

b) cUTI Patients

In addition to the 4 organisms listed in Table 13 as being the most prevalent for cUTI patients, there are also 10 infections total with *E. aerogenes* (4 in Cipro XR and 6 in Cipro BID) and 6 infections total with *P. aeruginosa* (3 in

each group). The bacteriologic eradication rates for these two additional organisms are shown in Table 22.

Reviewer's Comment: Table 22 was created by the reviewer.

TABLE 22
Bacteriological Eradication* at TOC Visit (+5 to +11 Days)
For cUTI Patients with Less Prevalent Organisms
(< 10 in Either Treatment Group)
Patients Valid for Efficacy

	n/N (%)	
	Cipro XR	Cipro BID
<i>Enterobacter aerogenes</i>	4/4 (100%)	6/6 (100%)
<i>Pseudomonas aeruginosa</i>	3/3 (100%)	3/3 (100%)

* n/N patients with specified baseline pathogen eradicated/patients with specified baseline pathogen

In the entire study population there are 15 isolates of *P. aeruginosa* identified in 15 patients (1 AUP patient and 14 cUTI patients), although only 6 are obtained from cUTI patients valid for efficacy. Due to the inherent resistance and increasing rates of emerging resistance to this organism in the community, a detailed evaluation of all 15 patients with *P. aeruginosa* isolated at baseline in the Cipro XR and Cipro BID groups was performed by the reviewer and the results are shown in Tables 23 and 24, respectively.

Reviewer's Comment: Tables 23 and 24 were created by the reviewer.

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On Original

TABLE 23
Cipro XR Patients with *Pseudomonas aeruginosa* as a Pathogen
in Pre-Therapy Urine Culture

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Valid for Efficacy?	<i>P. aeruginosa</i> MIC (µg/mL)	Bacteriological Response to <i>P. aeruginosa</i> at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
			If no, then reason				
AUP Patients							
209024	74/F	14	Yes	0.03	Eradication (Continued Eradication)	Cure (Continued Cure)	No
cUTI Patients							
041019	67/M	15	Yes	0.5	Eradication (Recurrence)	Cure (Continued Cure)	No
042046	74/M	14	No	> 16	Persistence (Persistence)	Cure (Not Reported)	No
			Resistant organism				
045002	68/F	8	No	> 16	Persistence and Superinfection with <i>E. faecalis</i> (Superinfection)	Not Reported (Not Reported)	Yes (amikacin and cefepime following TOC visit)
			Resistant organism				
045032	76/M	14	Yes	0.12	Eradication (Indeterminate)	Cure (Not Reported)	No
068010	44/M	7	No	16	Persistence (Persistence)	Failure (Failure)	Yes (Bactrim DS following TOC visit)
			Resistant organism				
101003	87/M	3	No	4	Indeterminate (Indeterminate)	Not Reported (Not Reported)	No
			No TOC urine culture; drug d/c due to dizziness as AE				
142017	79/M	11	Yes	0.12	Eradication (Continued Eradication)	Cure (Continued Cure)	No
151006	73/M	11	No	0.12	Indeterminate (Indeterminate)	Not Reported (Not Reported)	No
			No TOC urine culture; patient withdrew consent				

TABLE 24
Cipro BID Patients with *Pseudomonas aeruginosa* as a Pathogen
in Pre-Therapy Urine Culture

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Valid for Efficacy?	<i>P. aeruginosa</i> MIC (µg/mL)	Bacteriological Response to <i>P. aeruginosa</i> at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
cUTI Patients							
031024	81/M	14	Yes	0.12	Eradication (Eradication)	Cure (Continued Cure)	No
049031	83/M	14	Yes	0.25	Eradication (Recurrence)	Cure (Failure)	Yes (Macrobid following F/U visit, changed to Cipro)
064015*	81/M	12	No	0.25	Indeterminate (Indeterminate)	Not Reported (Not Reported)	No
			No TOC urine culture; patient withdrew consent				
076002	62/M	11	No	0.25	Eradication (New Infection with <i>S. aureus</i>)	Cure (Relapse)	Yes (Cipro following F/U visit)
			Protocol violation; did not have enough clinical symptoms for inclusion				
109002	52/M	12	Yes	0.12	Eradication of <i>P. aeruginosa</i> , but New Infection with <i>E. faecalis</i> (New Infection)	Cure (Not Reported)	Yes (ampicillin following F/U visit)
123003	67/M	15	No	4	Persistence (Persistence)	Cure (Relapse)	Yes (gentamicin following TOC visit)
			Resistant Organism				

* *E. faecalis* also present as pre-therapy pathogen

Reviewer's Comment: The applicant included Escherichia coli and Pseudomonas aeruginosa in the "Indications and Usage" section and in the efficacy table in the "Clinical Studies" section of the package insert. At a teleconference on July 10, 2003, the Division asked the applicant to provide information to support the inclusion of these two organisms in the label, since there are less than 10 isolates for each. On July 29, 2003 the applicant submitted the requested information. They indicated that they are withdrawing the proposal to include Escherichia coli in the "Indications and Usage" and "Clinical Studies" section and will shift the organism to the "second list" in the "Microbiology" section of the package insert.

Regarding the inclusion of P. aeruginosa in the XR label, the applicant justified their position with data to support the following: (1) immediate-release (IR) ciprofloxacin is indicated for cUTIs, including those caused by susceptible strains of P. aeruginosa, (2) an antimicrobial agent selected to treat cUTI should achieve adequate concentrations at the site of infection. Cipro XR 1000 mg tablets have an absolute bioavailability of up to 90% and a relative bioavailability of 98% when compared to the IR formulation. Plasma concentrations are about 40% to 70% greater than the concentrations achieved with 500 mg BID of the immediate-release formulation. In the urine, the XR formulation of ciprofloxacin (1000 mg) achieves significantly higher concentrations of ciprofloxacin than the immediate release formulation (500 mg BID) for up to 12 hours following a dose. Concentrations of both formulations in the urine remain in excess of the MIC values of susceptible pathogens throughout the dosing interval, (3) surveillance data shows that 75% of P. aeruginosa isolates from UTIs analyzed between Jan 1st and December 31st 2002, were susceptible to ciprofloxacin, and (4) nine of the 14 P. aeruginosa isolates identified in the pivotal trial (100275) are susceptible to ciprofloxacin. All nine were clinically cured and bacteriologically eradicated.

The applicant concludes that a combination of the microbiological data (MICs) for susceptible isolates of P. aeruginosa along with the achievable concentrations of the drug in plasma and urine, supports Cipro XR as an appropriate drug to select for the treatment of cUTI caused by susceptible strains of P. aeruginosa.

The applicant also indicated that they would be amenable to conducting a Phase IV study to gather additional isolates of P. aeruginosa, similar to what the Division requested of them for Staphylococcus saprophyticus for the indication of uUTI (Cipro XR 500 mg, NDA 21-473), if the Division would grant them P. aeruginosa in the label.

The reviewer accepts the applicant's rationale for inclusion of P. aeruginosa in the label, based on the pharmacokinetic and susceptibility data provided. In addition, the applicant will be requested to obtain information on additional isolates of P. aeruginosa as a Phase IV commitment.

4. By Duration of Therapy

Patients were assigned to treatment durations of 7 to 14 days by the individual investigators. Table 25 shows the eradication rates at the TOC visit subgrouped by the actual treatment duration (i.e., some patients took more or less medications than advised). Eradication rates are numerically similar (1) within treatment duration subgroups between study drugs; as well as, (2) within each study drug across different treatment duration subgroups.

Reviewer's Comment: Table 25 was created by the reviewer.

TABLE 25
Eradication (%) at the TOC Visit (+5 to +11 Days)
by Days of Treatment
Patients Valid for Efficacy

	Cipro XR	Cipro BID
<i>All Patients</i>	183/206 (88.8%)	195/229 (85.2%)
5 to 7 days	28/31 (90.3%)	24/30 (80.0%)
8 to 10 days	43/48 (89.6%)	43/52 (82.7%)
11 to 15 days	112/127 (88.2%)	128/147 (87.1%)
<i>AUP Patients</i>	35/40 (87.5%)	51/52 (98.1%)
5 to 7 days	3/3 (100%)	4/4 (100%)
> 7 to 10 days	5/7 (71.4%)	7/7 (100%)
10 to 14 days	27/30 (90%)	40/41 (97.6%)
<i>cUTI Patients</i>	148/166 (89.2%)	144/177 (81.4%)
5 to 7 days	25/28 (89.3%)	20/26 (76.9%)
> 7 to 10 days	38/41 (92.7%)	36/45 (80.0%)
10 to 15 days	85/97 (87.6%)	88/106 (83.0%)

Reviewer's Comment: There are two patients in the Cipro BID group that received less than 7 days of treatment (5 days and 6 days, respectively) in the applicant's valid for efficacy population. Both are cUTI patients with persistence of infection at the TOC visit.

5. By Timing of the TOC Visit

The original protocol specified the TOC visit should occur between 5 and 9 days following the last dose of study drug. Amendment number 7 expanded the TOC visit window from 5 to 9 days to 5 to 11 days after the last dose of study drug. An additional 17 patients are included in the valid for efficacy population when the TOC visit window was expanded from 9 days to 11 days after the last dose of study drug. Bacteriologic results for the 17 patients included in the expanded analysis are shown in Table 26. Table 27 presents bacteriologic response rates by timing of the TOC visit (i.e., response for the population with a TOC visit from 5 to 9 days versus 5 to 11 days after the last dose of study drug).

Reviewer's Comment: The applicant's October 29, 2002 submission stated there are an additional 19 patients included in the valid for efficacy population when the TOC visit window was expanded. However, the reviewer only identified 17 patients. In a correspondence dated May 2, 2003 the applicant corrected the number from 19 to 17 and provided a list of patients: 31004, 36003, 42028, 49011, 49057, 53001, 53013, 53018, 53028, 73010, 77018, 91002, 95018, 97001, 105011, 120001, 148019.

Reviewer's Comment: Tables 26 and 27 were created by the reviewer.

TABLE 26
Patients with the TOC visit Occurring between > 9 and 11 Days After the Last Dose of Study Drug

	Cipro XR (N=9)	Cipro BID (N=8)
Patients with bacteriologic eradication	7	7
cUTI patients eradicated	6/8	5/6
AUP patients eradicated	1/1	2/2
New infection	1 (cUTI)	0
Persistence	1 (cUTI)	1 (cUTI)

TABLE 27
Number of Patients (%) with Eradication by Timing of TOC Visit Patients Valid for Efficacy

	Cipro XR	Cipro BID
<i>All Patients</i>		
+5 to +9 days	176/197 (89.3%)	188/221 (85.1%)
+5 to +11 days	183/206 (88.8%)	195/229 (85.2%)
<i>AUP Patients</i>		
+5 to +9 days	34/39 (87.1%)	49/50 (98.0%)
+5 to +11 days	35/40 (87.5%)	51/52 (98.1%)
<i>cUTI Patients</i>		
+5 to +9 days	142/158 (89.9%)	139/171 (81.3%)
+5 to +11 days	148/166 (89.2%)	144/177 (81.4%)

B. Bacteremias

Of the 435 valid for efficacy patients, 429 (98.6%) had a pre-therapy blood culture obtained. Twelve of the 429 patients had bacteremia caused by *E. coli* (11 patients) and *K. pneumoniae* (1 patient) as shown in Table 28. There are two patients (patient 118021 in the Cipro XR group and patient 82040 in the Cipro BID group) out of the 12 patients with pre-therapy bacteremia in whom blood cultures were not performed at the during therapy visit. The organism isolated in blood was eradicated in 10/10 patients with during therapy blood culture results.

All 12 patients are bacteriologic cures (negative urine culture) and clinical cures at the TOC visit.

Reviewer's Comment: Table 28 was created by the reviewer.

TABLE 28
Patients with Pre-Therapy Bacteremia and Bacteriologic Outcome
Patients Valid for Efficacy

	n/N (%)	
	Cipro XR	Cipro BID
AUP Patients		
<i>Escherichia coli</i>	4/5*	1/1
<i>Klebsiella pneumoniae</i>	1/1	—
cUTI Patients		
<i>Escherichia coli</i>	1/1	3/4*

*one patient did not have a repeat blood culture during treatment

C. Organisms Causing Super and New Infections

A summary of the organisms causing superinfection or new infection in AUP and cUTI patients valid for efficacy at the TOC visit is presented in Table 29.

Appears This Way
 On Original

TABLE 29
Organisms Causing Superinfection or New Infections in
AUP and cUTI Patients Combined at TOC (+5 to +11 Days)
Patients Valid for Efficacy

	Cipro XR	Cipro BID
Superinfection		
<i>Staphylococcus aureus</i>	3	0
<i>Enterococcus faecalis</i>	0	1
<i>Klebsiella pneumoniae</i>	0	1
<i>Pseudomonas aeruginosa</i>	2	1
<i>Alcaligenes faecalis</i>	0	1
New Infection		
<i>Staphylococcus aureus</i>	1	4
<i>Enterococcus species</i>	0	1
<i>Enterococcus faecalis</i>	7	6
<i>Enterococcus faecium</i>	1	0
<i>Escherichia coli</i>	0	1
<i>Proteus mirabilis</i>	0	1
<i>Citrobacter freundii</i>	0	1
<i>Providencia stuartii</i>	1	0
<i>Acinetobacter calcoaceticus</i>	0	1
<i>Comamonas testosteroni</i>	1	0

The applicant indicated that the number of organisms causing superinfections (5 for Cipro XR and 4 for Cipro BID) or new infections (11 for Cipro XR and 15 for Cipro BID) is higher than shown in Table 10 for the corresponding bacteriologic response. This is due to some patients also having persistent organisms. These patients are classified as having a bacteriologic response of persistence and not superinfection or new infection.

There are more superinfections and new infections in the Cipro BID group (N=17 combined) compared to the Cipro XR group (N=10 combined) at the TOC visit for patients with cUTI. A detailed description of these patients can be found in Tables 30 and 31 for Cipro XR and Cipro BID, respectively.

<i>Reviewer's Comment: Tables 30 and 31 were created by the reviewer.</i>

TABLE 30
Cipro XR Patients with cUTI who Experienced
a Superinfection (N=5) or New Infection (N=5) at the TOC Visit
Patients Valid for Efficacy

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Urine Pathogen(s)	MIC (µg/mL)	Bacteriological Response at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
Superinfection							
31012	77/M	14	<i>E. faecalis</i> (pre-therapy)	1	Eradication (Indeterminate)	Failure (Failure)	Yes (gentamicin following TOC)
			<i>P. aeruginosa</i> ^a (TOC)	> 16	Superinfection (Superinfection)		
53027	25/F	15	<i>K. pneumoniae</i> (pre-therapy)	0.25	Eradication (Continued Eradication)	Cure (Continued Cure)	No
			<i>P. aeruginosa</i> (during therapy and TOC)	> 16	Superinfection (Superinfection)		
76013	83/F	14	<i>K. pneumoniae</i> (pre-therapy)	0.03	Indeterminate (Indeterminate)	Not Reported (Not Reported)	Yes (Macrobid following study drug)
			<i>E. faecium</i> (pre-therapy)	2	Indeterminate (Indeterminate)		
			<i>S. aureus</i> (during therapy)	> 16	Superinfection (Superinfection)		
90121*	96/F	7	<i>C. freundii</i> (pre-therapy)	0.12	Eradication (Continued Eradication)	Cure (Relapse)	Yes (Macrochantin at F/U, although F/U urine culture was negative)
			<i>P. mirabilis</i> (pre-therapy)	1	Eradication (Continued Eradication)		
			<i>Comamonas testasteroni</i> (TOC)	16	New infection (New infection)		
			<i>S. aureus</i> (during therapy and TOC)	> 16	Superinfection (Superinfection)		
127001	33/F	15	<i>E. faecalis</i> (pre-therapy)	2	Indeterminate (Indeterminate)	Failure (Failure)	Yes (Bactrim DS following study drug)
			<i>K. pneumoniae</i> (pre-therapy)	0.03	Indeterminate (Indeterminate)		
			<i>S. aureus</i> (during therapy)	> 16	Superinfection (Superinfection)		
New Infection							
15018	29/M	8	<i>P. mirabilis</i> (pre-therapy)	0.015	Eradication (Indeterminate)	Cure (Relapse)	Yes (Bactrim DS following TOC)
			<i>P. stuartii</i> ^c (TOC)	8	New Infection (New Infection)		
49057	75/F	14	<i>P. mirabilis</i> (pre-therapy)	0.06	Eradication (Continued Eradication)	Cure (Relapse)	Yes (Levo at F/U followed by Macrobid)
			<i>E. faecalis</i> (TOC and F/U)	> 16	New Infection (New Infection)		
			<i>E. coli</i> (F/U)	> 16	— (New Infection)		

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Urine Pathogen(s)	MIC (µg/mL)	Bacteriological Response at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
73011	41/F	10	<i>K. pneumoniae</i> (pre-therapy)	0.03	Eradication (Continued Eradication)	Cure (Continued Cure)	No
			<i>E. faecalis</i> (TOC and F/U)	1	New Infection (New Infection)		
125006	73/F	14	<i>K. pneumoniae</i> (pre-therapy)	0.25	Eradication (Indeterminate)	Failure (Failure)	Yes (Bactrim DS following study drug)
			<i>S. aureus</i> (TOC)	8	New Infection (New infection)		
207023	61/F	7	<i>E. coli</i> (pre-therapy)	0.015	Eradication (Continued Eradication)	Cure (Relapse)	Yes (Bactrim DS following TOC)
			<i>E. faecalis</i> (TOC and F/U)	> 16	New Infection (New Infection)		

* experienced both a superinfection and a new infection; counted as new infection only by the applicant

^a pre-therapy urine contained 6,000 CFU/mL of *P. aeruginosa* (regarded as contaminant)

TABLE 31
Cipro BID Patients with cUTI who Experienced
a Superinfection (N=3) or New Infection (N=14) at the TOC Visit
Patients Valid for Efficacy

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Urine Pathogen(s)	MIC (µg/mL)	Bacteriological Response at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
Superinfection							
35002	46/M	8	<i>P. mirabilis</i> ^a (pre-therapy)	0.12	Eradication (Recurrence)	Cure (Continued Cure)	No
			<i>E. faecalis</i> (during therapy)	1	Superinfection (Superinfection)		
			<i>P. mirabilis</i> ^b (F/U)	0.12	--		
90077	91/M	8	<i>P. mirabilis</i> (pre-therapy)	0.5	Indeterminate (Indeterminate)	Not Reported (Not Reported)	No
			<i>P. aeruginosa</i> ^c (during therapy)	> 16	Superinfection (Superinfection)		
			<i>K. pneumoniae</i> (during therapy)	> 16	Superinfection (Superinfection)		
127007	32/M	14	<i>Providencia rettgeri</i> (pre-therapy)	0.03	Indeterminate (Continued Eradication)	Cure (Continued Cure)	No
			<i>Alcaligenes faecalis</i> (during therapy)	> 16	Superinfection (Superinfection)		
			<i>P. aeruginosa</i> (F/U)	2	Superinfection (New Infection)		
New Infection							
15003	47/M	7	<i>E. coli</i> (pre-therapy)	0.12	Eradication (Indeterminate)	Cure (Not Reported)	Yes (Bactrim DS following)

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Urine Pathogen(s)	MIC (µg/mL)	Bacteriological Response at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
			<i>S. aureus</i> (TOC)	> 16	New Infection (New Infection)		TOC)
15016	32/M	7	<i>P. mirabilis</i> (pre-therapy)	0.03	Eradication (Indeterminate)	Cure (Not Reported)	Yes (Bactrim DS following TOC)
			<i>S. aureus</i> (TOC)	16	New Infection (New Infection)		
29042	37/F	14	<i>S. aureus</i> (pre-therapy)	0.5	Eradication (Continued Eradication)	Cure (Continued Cure)	No
			<i>E. faecalis</i> (TOC and F/U)	1	New Infection (New Infection)		
39005	75/M	7	<i>E. faecalis</i> (pre-therapy)	1	Eradication (Indeterminate)	Cure (Not Reported)	No
			<i>S. aureus</i> (TOC)	> 16	New Infection (New Infection)		
42022	81/M	14	<i>E. coli</i> (pre-therapy)	1	Eradication (Indeterminate)	Cure (Not Reported)	No
			<i>E. faecalis</i> (TOC)	0.5	New Infection (New Infection)		
48013	72/F	15	<i>E. coli</i> (pre-therapy)	0.03	Eradication (Indeterminate)	Failure (Failure)	No
			<i>E. faecalis</i> (TOC)	> 16	New Infection (New Infection)		
59033	63/F	7	<i>K. pneumoniae</i> (pre-therapy)	0.5	Eradication (Indeterminate)	Failure (Failure)	Yes (Bactrim DS at TOC)
			<i>E. coli</i> (TOC)	> 16	New Infection (New Infection)		
74002	87/F	14	<i>P. mirabilis</i> (pre-therapy)	2	Eradication (Recurrence)	Cure (Continued Cure)	No
			<i>E. faecalis</i> (TOC)	> 16	New Infection (New Infection)		
			<i>P. mirabilis</i> (F/U)	2	-		
76008	90/M	10	<i>Citrobacter koseri</i> (pre-therapy)	0.015	Eradication (Indeterminate)	Cure (Relapse)	Yes (Macrobid following TOC)
			<i>E. faecalis</i> (TOC)	> 16	New Infection (New Infection)		
92011	82/F	14	<i>S. marcescens</i> (pre-therapy)	1	Eradication (Indeterminate)	Failure (Failure)	No
			<i>E. faecalis</i> (pre-therapy)	1	Eradication (Indeterminate)		
			<i>P. mirabilis</i> (TOC)	2	New Infection (New Infection)		
95009	57/F	14	<i>K. pneumoniae</i>	0.06	Eradication (Continued Eradication)	Cure (Failure)	Yes (Macrobid at F/U)
			<i>Acinetobacter calcoaceticus</i> (TOC)	Not reported	New Infection (New Infection)		

Patient No.	Age (yr)/Sex	Treatment Duration (d)	Urine Pathogen(s)	MIC (µg/mL)	Bacteriological Response at TOC (at F/U)	Clinical Response at TOC (at F/U)	Alternative Antibiotic (Yes/No)
			<i>Enterococcus</i> sp. (TOC)	Not reported	New Infection (New Infection)		
			<i>E. faecalis</i> (F/U)	0.5	–		
			<i>E. coli</i> (F/U)	0.12	–		
109002	52/M	12	<i>P. aeruginosa</i> (pre-therapy)	0.12	Eradication (Indeterminate)	Cure (Not Reported)	Yes (Ampicillin at following TOC)
			<i>E. faecalis</i> (TOC)	> 16	New Infection (New Infection)		
115001	30/M	14	<i>K. pneumoniae</i> ¹ (pre-therapy)	0.06	Eradication (Indeterminate)	Cure (Not Reported)	Yes (Doxycycline following TOC)
			<i>C. freundii</i> ⁹ (TOC)	4	New Infection (New Infection)		
137002	50/F	14	<i>E. coli</i> (pre-therapy)	0.015	Eradication (Continued Eradication)	Cure (Continued Cure)	No
			<i>S. aureus</i> (TOC)	> 16	New Infection (New Infection)		

^a Pre-therapy urine culture also contained 60,000 CFU/mL of *E. cloacae* (MIC 0.015 µg/mL)

^b F/U urine culture also contained 20,000 *E. faecalis* (MIC 0.5 µg/mL)

^c During therapy urine culture also contained 20,000 *E. faecalis* (MIC > 16 µg/mL)

^d TOC urine culture also contained 35,000 CFU/mL of *P. mirabilis* (MIC 0.03 µg/mL)

^e Pre-therapy urine culture also contained 50,000 CFU/mL of *S. marcescens* (0.12 µg/mL)

^f Pre-therapy urine culture also contained 20,000 CFU/mL of *E. faecalis* (MIC 1 µg/mL)

^g TOC urine culture also contained 15,000 CFU/mL of *Acinetobacter* sp. (MIC 4 µg/mL)

D. Eradication at the Late Follow-up Visit

Bacteriological response at the late follow-up visit (+28 to +42 days) is a secondary efficacy variable and the results are shown in Table 32. Eradication is 69.3% in the Cipro XR group and 61.2% in the ciprofloxacin BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (-0.8%, 18.6%) is above -10%. The 95% confidence interval using the normal approximation to the binomial distribution with continuity correction is (-2.2%, 18.4%).

Reviewer's Comment: Patients with indeterminate responses are specified in the protocol as excluded from valid for efficacy analysis. Therefore, the eradication rates at follow-up in this analysis population do not include the 68 indeterminate responses (27/206 [13.1%] in the Cipro XR group and 41/229 [17.9%] in the Cipro BID group).

TABLE 32
Number of Patients (%) with Bacteriological Response at the
Follow-up Visit (+28 to +42 Days)
Patients Valid for Efficacy

	Cipro XR	Cipro BID
<i>All Patients</i>	(N=206)	(N=229)
Continued eradication	124 (60.2%)	115 (50.2%)
Eradication w/recurrence	19 (9.2%)	18 (7.9%)
Persistence	10 (4.9%)	17 (7.4%)
Superinfection	5 (2.4%)	2 (0.9%)
New infection	21 (10.2%)	36 (15.7%)
Indeterminate	27 (13.1%)	41 (17.9%)
Eradication Rate^a	124/179 (69.3%)	115/188 (61.2%)
<i>AUP Patients</i>	(n=40)	(n=52)
Continued eradication	25 (62.5%)	35 (67.3%)
Eradication w/recurrence	1 (2.5%)	3 (5.8%)
Persistence	2 (5.0%)	1 (1.9%)
New infection	5 (12.5%)	4 (7.7%)
Indeterminate	7 (17.5%)	9 (17.3%)
Continued Eradication Rate^b	25/33 (75.8%)	35/43 (81.4%)
<i>cUTI Patients</i>	(n=166)	(n=177)
Continued eradication	99 (59.6%)	80 (45.2%)
Eradication w/recurrence	18 (10.8%)	15 (8.5%)
Persistence	8 (4.8%)	16 (9.0%)
Superinfection	5 (3.0%)	2 (1.1%)
New infection	16 (9.6%)	32 (18.1%)
Indeterminate	20 (12.0%)	32 (18.1%)
Continued Eradication Rate^c	99/146 (67.8%)	80/145 (55.2%)

^a Eradication rate for all patients (cUTI plus AUP); the follow-up rates in this population do not include the indeterminate responses. 95% Confidence Interval: (-0.8%, 18.6%)

^b Continued eradication rate for AUP patients, not including indeterminate responses.

^c Continued eradication rate for cUTI patients, not including indeterminate responses.

The bacteriologic eradication rates at the late follow-up visit in AUP patients are lower in the Cipro XR group (62.5%, 25/40) compared to the Cipro BID group (67.3%, 35/52). In cUTI patients, the rates are higher in the Cipro XR group (59.6%, 99/166) compared to the Cipro BID group (45.2%, 80/177). The differences between the two patient groups follows a similar trend to the results at the TOC visit.

Reviewer's Comment: For the analysis of bacteriologic eradication at the late follow-up visit performed on the MITT population (all patients with a pathogen identified at baseline), see statistical review (Ruthana Davi, M.S., statistical reviewer).

Reviewer's Comment: One patient in the Cipro BID group (35002) who was counted in the superinfection category at the TOC visit (see Table 10) was

subsequently counted in the category eradication with recurrence (not superinfection) at the follow-up visit (see Table 26). The baseline pathogen for this patient was *P. mirabilis*, and *E. faecalis* was isolated during therapy (superinfection). At the TOC visit, *P. mirabilis* was eradicated and *E. faecalis* was absent. At the follow-up visit, *P. mirabilis* again was isolated from urine, and the patient was included in the response category eradication with recurrence by the applicant rather than being carried forward as superinfection. The reviewer agrees with this assessment.

Reviewer's Comment: For the analysis of bacteriologic eradication at the late follow-up visit performed on the MITT population (all patients with a pathogen identified at baseline), see statistical review (Ruthana Davi, M.S., statistical reviewer).

E. By Organism

The bacteriologic response rates by organism at the follow-up visit in patients valid for efficacy are shown in Table 33.

TABLE 33
Bacteriological Response at Follow-up (+28 to +42 Days) by Organism
Patients Valid for Efficacy

	n/N (%)	
	Cipro XR	Cipro BID
AUP Patients		
<i>Escherichia coli</i>	27/28 (96%)	33/34 (97%)
cUTI Patients		
<i>Escherichia coli</i>	74/87 (85%)	60/72 (83%)
<i>Klebsiella pneumoniae</i>	13/16 (81%)	12/16 (75%)
<i>Enterococcus faecalis</i>	10/12 (83%)	7/16 (44%)
<i>Proteus mirabilis</i>	9/11 (82%)	6/8 (75%)

Except for *E. coli*, eradication rates for patients with cUTI are slightly higher in the Cipro XR group than in the Cipro BID group. In both treatment arms, eradication rates decreased from the TOC time point to the follow-up time point.

F. Organisms Causing Super and New Infections

A summary of the organisms causing superinfection or new infection in patients valid for efficacy at follow-up is presented in Table 34. The results include the numbers of superinfections and new infections at the TOC carried forward as well as superinfections and new infections at follow-up.

Reviewer's Comment: Table 34 is modified from the applicant's submission by the reviewer for clarity.

TABLE 34
Organisms Causing Superinfection or New Infections at Follow-up (+28 to +42 Days) Patients Valid for Efficacy

	Cipro XR	Cipro BID
Superinfection		
<i>S. aureus</i>	3	0
<i>E. faecalis</i>	0	1
<i>K. pneumoniae</i>	0	1
<i>P. aeruginosa</i>	2	1
<i>A. faecalis</i>	0	1
New Infection		
<i>S. aureus</i>	4	4
<i>S. saprophyticus</i>	1	0
<i>Enterococcus sp.</i>	0	2
<i>E. faecalis</i>	14	17
<i>E. faecium</i>	1	0
<i>E. coli</i>	4	4
<i>K. pneumoniae</i>	0	7
<i>K. oxytoca</i>	1	0
<i>P. mirabilis</i>	0	1
<i>C. freundii</i>	1	2
<i>C. amalonaticus</i>	0	1
<i>P. stuartii</i>	1	0
<i>P. aeruginosa</i>	1	2
<i>A. calcoaceticus</i>	0	1
<i>C. testosteroni</i>	1	0

The number of organisms causing superinfections (5 for Cipro XR and 4 for Cipro BID) or new infections (29 for Cipro XR and 41 for Cipro BID) is higher than shown in Table 32 for the corresponding bacteriologic response. This is due to some patients also having persistent organisms. These patients are classified as having a bacteriologic response of persistence and not superinfection or new infection.

Of the 39 new infecting organisms recovered after the TOC time point, 18 are identified as *E. faecalis* (7 from patients in the Cipro XR group and 11 from patients in the Cipro BID group), 7 are identified as *E. coli* (4 and 3, respectively) and 7 are identified as *K. pneumoniae* (0 and 7, respectively). There are more patients in the Cipro BID group than in the Cipro XR group who had new infecting organisms isolated between the TOC and follow-up visits (17 in the Cipro XR group versus 26 in the Cipro BID group).

VI. Efficacy Results for the Valid for Efficacy Population – Clinical Response

A. Clinical Response at the TOC Visit

The clinical response rate at the TOC visit is a secondary efficacy parameter and the results in patients valid for efficacy are shown in Table 35. Eradication is 96.6% in the Cipro XR group and 93.8% in the ciprofloxacin BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (-1.2%, 6.9%) is above -10%. The 95% confidence interval using the normal approximation to the binomial distribution with continuity correction is (-1.7%, 7.3%).

TABLE 35
Number of Patients (%) with Clinical Response
at the TOC Visit (+5 to +11 Days)
Patients Valid for Efficacy

	Cipro XR	Cipro BID
<i>All Patients</i>	(N=206)	(N=229)
Cure	198 (96.1%)	211 (92.1%)
Failure	7 (3.4%)	14 (6.1%)
Indeterminate	0 (0.0%)	1 (0.4%)
Missing	1 (0.5%)	3 (1.3%)
Success Rate^a	198/205 (96.6%)	211/225 (93.8%)
<i>AUP Patients</i>	(n=40)	(n=52)
Cure	39 (97.5%)	50 (96.2%)
Failure	1 (2.5%)	2 (3.8%)
<i>cUTI Patients</i>	(n=166)	(n=177)
Cure	159 (95.8%)	161 (91.0%)
Failure	6 (3.6%)	12 (6.8%)
Indeterminate	0 (0.0%)	1 (0.6%)
Missing	1 (0.6%)	3 (1.7%)
Success Rate^b	159/165 (96.4%)	161/173 (93.1%)

^a Success rate for all patients (cUTI plus AUP), not including indeterminate or missing responses; 95% Confidence Interval: (-1.2%, 6.9%)

^b Success rate for patients with cUTI, not including indeterminate or missing responses

Reviewer's Comment: The clinical cure rates for AUP and cUTI patients separately were calculated by the statistical reviewer.

The clinical cure rates for the AUP patients are similar in the Cipro XR group (97.5%) to the Cipro BID group (96.2%) [corresponding 97.5% confidence interval of the difference (-15.3%, 21.1%)]. In the cUTI group clinical cure rates are also similar between the Cipro XR group (95.8%) and the Cipro BID group (91.0%) [corresponding 97.5% confidence interval of the difference* (-1.1, 10.8%)]. *When calculating the results of each stratum alone an adjustment must be made for multiple comparisons (i.e., use of 97.5% confidence intervals for the differences between Cipro XR and Cipro BID within the AUP and cUTI subgroups).*

Reviewer's Comments: Patients with indeterminate responses are specified in the protocol as excluded from valid for efficacy analysis. Only one cUTI patient in the Cipro BID group had an indeterminate clinical response at the TOC visit.

Each of the clinical signs and symptoms present initially must be rated as 0 (none present) in order to be considered a clinical cure. In a few of the 10% random sample, the patients considered to be clinical cures by the Investigator still had signs and or symptoms present at the TOC visit that were present at baseline, but these may have been due to the patient's underlying condition(s) and not infection.

The results for clinical response are consistent with the results for bacteriological response within treatment groups for the category "All Patients" in the valid for efficacy population at the TOC visit as seen in Table 36. However, for patients with AUP who were treated with Cipro XR, there is a 10% difference between the eradication rate (87.5%) and the clinical cure rate (97.5%) at the TOC visit.

Reviewer's Comment: Table 36 was created by the reviewer.

TABLE 36
Comparison of Bacteriologic and Clinical Success Rates
at the TOC Visit (+5 to +11 Days)
Patients Valid of Efficacy

	n/N (%)			
	Cipro XR		Cipro BID	
	Bacteriologic	Clinical	Bacteriologic	Clinical
All Patients	183/260 (88.8)	198/205 (96.6)	195/229 (85.2)	211/225 (93.8)
AUP Patients	35/40 (87.5)	39/40 (97.5)	51/51 (98.1)	50/52 (96.2)
cUTI Patients	148/166 (89.2)	159/165 (96.4)	144/177 (81.4)	161/173 (93.1)

A summary of clinical response by bacteriological response at the TOC visit for patients valid for efficacy is shown in Table 37. There are somewhat fewer discordant observations in the Cipro XR group than in the Cipro BID group. For 91% of patients in the Cipro XR group and 88% of patients in the Cipro BID group, the clinical and bacteriological response assessments are both either successful outcomes or unsuccessful outcomes.

TABLE 37
Clinical Response by Bacteriological Response
at the TOC Visit (+5 to +11 Days)
Patients Valid for Efficacy

Bacteriological Response	Clinical Response	Cipro® XR	Cipro® BID
Eradication	Cure	182 (99.5%)	191 (97.9%)
	Failure	1 (0.5%)	3 (1.5%)
	Indeterminate	0 (0.0%)	1 (0.5%)
Persistence	Cure	7 (70.0%)	7 (41.2%)
	Failure	3 (30.0%)	8 (47.1%)
	Missing	0 (0.0%)	2 (11.8%)
Superinfection	Cure	2 (40.0%)	2 (66.7%)
	Failure	2 (40.0%)	0 (0.0%)
	Missing	1 (20.0%)	1 (33.3%)
New infection	Cure	7 (87.5%)	11 (78.6%)
	Failure	1 (12.5%)	3 (21.4%)

B. Clinical Response at the Follow-up Visit

The clinical response rate at the follow-up visit is a secondary efficacy parameter and the results in patients valid for efficacy is shown in Table 38. Eradication is 82.9% in the Cipro XR group and 80.8% in the ciprofloxacin BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (-5.4%, 10.4%) is above -10%. The 95% confidence interval using the normal approximation to the binomial distribution with continuity correction is (-6.3%, 10.6%).

Reviewer's Comment: Patients with indeterminate responses are specified in the protocol as excluded from valid for efficacy analysis. Therefore, the eradication rates at follow-up in this analysis population do not include the 68 indeterminate responses (27/206 [13.1%] in the Cipro XR group and 41/229 [17.9%] in the Cipro BID group).

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TABLE 38
Number of Patients (%) with Clinical Response at the
Follow-up Visit (+28 to +42 Days)
Patients Valid for Efficacy

	Cipro XR	Cipro BID
<i>All Patients</i>	(N=206)	(N=229)
Continued cure	150 (72.8%)	151 (65.9%)
Failure	8 (3.9%)	16 (7.0%)
Relapse	23 (11.2%)	20 (8.7%)
Indeterminate	2 (1.0%)	3 (1.3%)
Missing	23 (11.2%)	39 (17.0%)
Success Rate^a	150/181 (82.9%)	151/187 (80.8%)
<i>AUP Patients</i>	(n=40)	(n=52)
Continued cure	30 (75.0%)	42 (80.8%)
Failure	1 (2.5%)	2 (3.8%)
Relapse	5 (12.5%)	0 (0.0%)
Missing	4 (10.0%)	8 (15.4%)
Success Rate^b	30/36 (83.3%)	42/44 (95.5%)
<i>cUTI Patients</i>	(n=166)	(n=177)
Continued cure	120 (72.3%)	109 (61.6%)
Failure	7 (4.2%)	14 (7.9%)
Relapse	18 (10.8%)	20 (11.3%)
Indeterminate	2 (1.2%)	3 (1.7%)
Missing	19 (11.4%)	31 (17.5%)
Success Rate^c	120/145 (82.8%)	109/143 (76.2%)

^a Success rate for all patients (cUTI plus AUP), not including missing or indeterminate responses; 95% Confidence Interval: (-5.4%, 10.4%)

^b Success rate for pyelonephritis patients, not including missing responses.

^c Success rate for complicated UTI patients, not including missing or indeterminate responses.

The clinical response at the late follow-up visit in AUP patients is slightly lower for the Cipro XR group (75%, 30/40) compared to Cipro BID group (80.8%, 42/52). In cUTI patients, the response rates are slightly higher in the Cipro XR group (72.3%, 120/166) compared to the Cipro BID group (61.6%, 109/177).

The results for clinical response are lower than the results for bacteriological response in the valid for efficacy population at the follow-up visit as seen in Table 39.

<i>Reviewer's Comment: Table 39 was created by the reviewer.</i>
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TABLE 39
Comparison of Bacteriologic and Clinical Success Rates
at the Follow-Up Visit (+28 to +42 Days)
Patients Valid of Efficacy

	n/N (%)			
	Cipro XR		Cipro BID	
	Bacteriologic	Clinical	Bacteriologic	Clinical
All Patients	124/179 (69.3)	150/181 (82.9)	115/188 (61.2)	151/187 (80.8)
AUP Patients	25/33 (75.8)	30/36 (83.3)	35/43 (81.4)	42/44 (95.5)
cUTI Patients	99/146 (67.8)	120/145 (82.8)	80/145 (55.5)	109/143 (76.2)

VII. Post-Treatment Antimicrobial Use

Twenty-three (23) percent of patients valid for efficacy in both treatment groups used at least one post-treatment antimicrobial agent at some point from one day after the end of therapy through the end of the long-term follow-up period. Antimicrobials were used for urinary tract infections as well as other types of infections. The most common post-therapy antimicrobial drugs used were ciprofloxacin (7% in Cipro XR group and 8% in Cipro BID group), nitrofurantoin (6% in the Cipro XR group and 4% in the Cipro BID group), and levofloxacin (5% in the Cipro XR group and 3% in the Cipro BID group).

VIII. Efficacy Results for the Applicant's Valid for Safety (Intent to Treat) Population – Bacteriologic and Clinical Response

Efficacy variables for patients valid for safety are presented in Tables 40-43 in Appendix 2. The main differences between the valid for safety population and the valid for efficacy population occurred in the bacteriological responses and clinical responses at the TOC visit. In the valid for safety analysis population, eradication rates at the TOC visit are 63.3% and 67.9% in the Cipro XR and Cipro BID group, respectively, as shown in Table 40. The 95% confidence interval for the difference in response between the two treatments at this time point is (-11.8%, 2.9%). The clinical cure rates at the TOC visit are 66.3% and 70.9% for the respective treatment groups as shown in Table 42 and the 95% confidence interval is (-10.1%, 1.2%).

These differences are caused mainly by inclusion of indeterminate bacteriological responses and indeterminate or missing clinical responses that are excluded from the analyses of the valid for efficacy population. The Cipro XR group has more patients with an indeterminate bacteriological response at TOC as compared to the Cipro BID group (82 [25.1%] versus 49 [15.6%] patients; Table 40). Approximately 50% of the patients have data outside the window for the TOC visit or have no data at the TOC visit. Although the Cipro BID group has a higher percentage of patients with an outcome of persistence, superinfection, or new infection (38 [11.6%] in the Cipro XR group versus 52 [16.5%] in the Cipro BID group), the inclusion of indeterminate responses as nonsuccesses lowered the eradication rate disproportionately in the Cipro XR group.

The clinical cure rate at TOC is affected in a similar manner by inclusion of missing clinical responses as nonsuccesses. More patients in the Cipro XR group (138 [26.7%]) than in the Cipro BID group (111 [21.4%]; Table 36) have a missing or indeterminate clinical response. Therefore, the clinical cure rate appeared to be lower in the Cipro XR treatment group.

The discrepancy between the two treatment groups in terms of the distribution of patients with missing or indeterminate responses is still present, but to a lesser extent, at follow-up for the valid for safety population.

IX. Efficacy Results for Special Populations – Bacteriologic Response

Subgroup analyses were performed on data for the valid for efficacy population to explore potential drug-demographic interactions based on age, sex, and race.

A. Age

Bacteriological response by age at the TOC visit is summarized in Table 44. For patients treated with Cipro XR, the bacteriologic eradication rates are lower in patients less than 65 years of age [85.0% (85/100)] compared to those 65 years of age and older [92.4% (98/106)] at the TOC visit. Less efficacy in the younger patients may be a result of the lower bacteriological response in AUP patients [87.5% (935/40)] compared to cUTI patients [89.2% (148/166)]. Patients treated with Cipro XR in the AUP sub-group are younger (mean age 41 years) compared with cUTI (mean age 64 years).

Although younger patients treated with Cipro XR have lower eradication rates [85.0% (85/100)] than older patients treated with Cipro XR, the efficacy in this age group is similar to patients treated with Cipro BID [84.1% (90/107)]. Patients receiving Cipro BID responded similarly, regardless of age [84.1% (90/107) eradication for those < 65 years and 86.1% (105/122) for those ≥ 65 years].

Reviewer's Comment: The differences seen in bacteriologic eradication between younger and older patients is not considered clinically relevant and no adjustments to the dosing of Cipro XR are warranted based on age.

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TABLE 44
Number of Patients (%) with Bacteriological Response by Age (in years) at the
TOC Visit (+5 to +11 Day)
Patients Valid for Efficacy

	Cipro XR				Cipro BID			
	< 65 N=100	≥ 65 N=106	65-74 N=44	≥ 75 N=62	<65 N=107	≥ 65 N=122	65-74 N=49	≥ 75 N=73
Eradication	85 (85.0)	98 (92.4)	42 (95.5)	56 (90.3)	90 (84.1)	105 (86.1)	40 (81.6)	65 (89.0)
Persistence	7 (7.0)	3 (2.8)	1 (2.3)	2 (3.2)	7 (6.5)	10 (8.2)	8 (16.3)	2 (2.7)
Superinfection	2 (2.0)	3 (2.8)	0 (0.0)	3 (4.8)	2 (1.9)	1 (0.8)	0 (0.0)	1 (1.4)
New Infection	6 (6.0)	2 (1.9)	1 (2.3)	1 (1.6)	8 (7.5)	6 (4.9)	1 (2.0)	5 (6.8)

B. Sex

Bacteriological response by sex at the TOC visit is summarized in Table 45. Male patients [92.0% (81/88)] have a higher bacterial eradication rate than female patients [86.4% (102/118)] treated with Cipro XR at the TOC visit. The reverse situation is true for Cipro BID where female patients [89.8% (114/127)] have a higher eradication rate than male patients [79.4% (81/102)]. The difference in the Cipro XR group appears to be due to a higher number of female patients with superinfections and new infections.

Although the female patients treated with Cipro XR have lower eradication rates [86.4% (102/118)] than male patients treated with Cipro XR, the efficacy in this group is similar to female patients treated with Cipro BID [89.8% (114/127)] and higher than male patients treated with Cipro BID [79.4% (81/102)].

Reviewer's Comment: The differences seen in bacteriologic eradication between males and females patients is not considered clinically relevant and no adjustments to the dosing of Cipro XR are warranted based on sex.

TABLE 45
Number of Patients (%) with Bacteriological Response by Sex at the
TOC Visit (+5 to +11 Day)
Patients Valid for Efficacy

	Cipro XR		Cipro BID	
	Male N=88	Female N=118	Male N=102	Female N=127
Eradication	81 (92.0%)	102 (86.4%)	81 (79.4%)	114 (89.8%)
Persistence	5 (5.7%)	5 (4.2%)	11 (10.8%)	6 (4.7%)
Superinfection	1 (1.1%)	4 (3.4%)	3 (2.9%)	0 (0.0%)
New Infection	1 (1.1%)	7 (5.9%)	7 (6.9%)	7 (5.5%)

C. Race

Bacteriological response by race at the TOC visit is summarized in Table 46. Most of the valid for efficacy patients are Caucasian [79% (345/435)]. Among patients who are not Caucasian, most are categorized as Black or Hispanic [20% (88/435)]. Less than 1% of patients in each treatment group are Asian. Eradication rates for both Cipro XR and Cipro BID appear similar for Caucasian and Black patients. Hispanic patients appear to have higher eradication rates. There are too few Asian patients in the study to make an assessment on eradication.

Reviewer's Comment: The differences seen in bacteriologic eradication between patients of different ethnic backgrounds are not considered clinically relevant and no adjustments to the dosing of Cipro XR are warranted based on race.

TABLE 46
Number of Patients (%) with Bacteriological Response by Race
at the TOC Visit (+5 to +11 Day)
Patients Valid for Efficacy

	Cipro XR			
	Caucasian N=168	Asian N=1	Hispanic N=18	Black N=19
Eradication	148 (88.1%)	1 (100.0%)	17 (94.4%)	17 (89.5%)
Persistence	10 (6.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Superinfection	4 (2.4%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
New infection	6 (3.6%)	0 (0.0%)	1 (5.6%)	1 (5.3%)
	Cipro BID			
	Caucasian N=177	Asian N=1	Hispanic N=24	Black N=27
Eradication	149 (84.2%)	1 (100.0%)	23 (95.8%)	22 (81.5%)
Persistence	16 (9%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
Superinfection	3 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
New infection	9 (5.1%)	0 (0.0%)	1 (4.2%)	4 (14.8%)

X. Safety Analyses

Of the 1042 patients enrolled into the study, 1035 received at least one dose of study drug (517 in the Cipro XR group and 518 in the Cipro BID group). Seven patients (4 in the Cipro XR group and 3 in the Cipro BID group) are not included in the valid for safety population because study drug administration in these patients could not be documented.

A. Overview

An overview of patients who experienced various safety events is summarized in Table 47. The proportion of patients who experienced at least one adverse event (31.9%) is the same in both treatment groups. In addition, rates of drug-related events, serious events, and premature discontinuation due to adverse events are nearly the same in both treatment groups. More patients in the Cipro XR group

(28 patients) than in the Cipro BID group (19 patients) discontinued study drug due to an adverse event.

TABLE 47
Summary of Adverse Events
Patients Valid for Safety

	Cipro XR (N=517)	Ciprofloxacin BID (N=518)
Survived	514 (99.4%)	517 (99.8%)
Any adverse event	165 (31.9%)	165 (31.9%)
Any drug-related adverse event	68 (13.2%)	70 (13.5%)
Any serious adverse event	28 (5.4%)	25 (4.8%)
Discontinuation due to adverse event	28 (5.4%)	19 (3.7%)

Reviewer's Comment: The applicant has proposed to reduce the dosage of Cipro XR 1000 mg in patients with severe renal impairment to Cipro XR 500 mg. This is acceptable to the FDA Clinical Pharmacology and Biopharmaceutics reviewer. However, the issue of dosage adjustment of Cipro XR 1000 mg in cUTI and AUP patients with mild to moderate renal impairment has not been addressed by the applicant in this NDA. Since there is no pharmacokinetic data in patients with mild to moderate renal impairment, it is unknown if the C_{max} and AUC following administration of Cipro XR 1000 mg would result in excessive drug exposure and a higher incidence of adverse events.

To address this question, the reviewer compared the adverse events reported for patients in the valid for safety population with normal renal function [i.e., a creatinine clearance (CLcr) above 80 mL/min] to the adverse events reported for those with mild to moderate renal impairment [CLcr from 50 to 50 mL/min] in both treatment arms of the study. In Appendix 2, Tables 47A and 47B provide an overview of adverse events in these two subgroups and Tables 48A and 48B detail specific events occurring in at least two patients per treatment arm within the subgroups.

Upon review of these data, the reviewer does not feel that the overall incidence of adverse events or incidence of specific adverse events is different between the two subgroups. In conjunction with the Clinical Pharmacology and Biopharmaceutics reviewer (Dakshina Chilukuri, Ph.D.), the reviewer felt that for AUP and cUTI patients with mild to moderate renal impairment, no dosage adjustment if Cipro XR 1000 mg is recommended, at this time. The applicant will be asked to perform Monte-Carlo simulations to simulate exposure of Cipro XR 1000 mg (administered once daily for 14 days) to patients with mild and moderate renal impairment as a Phase IV commitment. Based on these results, changes in labeling may be recommended at a later time.

B. Adverse Events

A summary of adverse events by body system for each treatment group is presented in Table 49. The most common adverse events in both treatment groups occur in the digestive body system. The incidence of adverse events for

each body system is similar between treatment groups, except for the nervous system. Six percent (6%) of patients in the Cipro XR group (30 patients) experienced at least one adverse event involving the nervous system compared with 4% (20 patients) in the of Cipro BID group. The events primarily responsible for this difference are dizziness (16 patients [3%] in the Cipro XR group versus 10 patients [2%] in the Cipro BID group), and abnormal dreams, depression, hallucinations, stupor, thinking abnormal, tremor, and hypesthesia (1 patient for each [$<1\%$] versus 0 patients [0%], respectively).

TABLE 49
Incidence Rates of Adverse Events by Body System
Patients Valid for Safety

Body System	Cipro XR (N=517)		Cipro BID (N=518)	
Any body system	165	(32%)	165	(32%)
Body as a whole	54	(10%)	58	(11%)
Cardiovascular	20	(4%)	16	(3%)
Digestive	71	(14%)	67	(13%)
Hemic and lymphatic	5	(<1%)	4	(<1%)
Metabolic & nutritional	8	(2%)	3	(<1%)
Musculoskeletal	6	(1%)	12	(2%)
Nervous	30	(6%)	20	(4%)
Respiratory	19	(4%)	21	(4%)
Skin and appendages	10	(2%)	10	(2%)
Special senses	7	(1%)	5	(<1%)
Urogenital	39	(8%)	34	(7%)

A summary of adverse events experienced by at least 2% of patients in at least one treatment group is presented in Table 50. The incidence of patients with adverse events generally is similar between treatment groups, with no event having more than a 1% difference between groups, except for headache (3% in the Cipro XR group versus 5% in the Cipro BID group).

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TABLE 50
Incidence Rates of Adverse Events Occurring in at Least 2% of Patients
in Either Treatment Group
Patients Valid for Safety

Adverse Event	Cipro XR (N=517)		Cipro BID (N=518)	
Any Body System				
Any event	165	(32%)	165	(32%)
Body as a Whole				
Headache	17	(3%)	25	(5%)
Digestive				
Nausea	24	(5%)	23	(4%)
Diarrhea	15	(3%)	11	(2%)
Vomiting	14	(3%)	8	(2%)
Dyspepsia	9	(2%)	6	(1%)
Constipation	5	(<1%)	9	(2%)
Nervous				
Dizziness	16	(3%)	10	(2%)
Urogenital				
Vaginal moniliasis	10	(2%)	8	(2%)

C. Drug-Related Adverse Events

Drug-related adverse events are defined as events considered by the investigator to be possibly or probably related to study drug. Sixty-eight (68) of the 165 patients in the Cipro XR group and 70 of the 165 patients in the Cipro BID group who experienced treatment-emergent adverse events had at least one event that was assessed by the investigator as possibly or probably related to study drug. A summary of drug-related adverse events experienced by at least 1% of patients in either treatment group is presented in Table 51. The incidence rates of drug-related adverse events are similar between the two treatment groups. Nausea and diarrhea are the most common drug-related adverse events.

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TABLE 51
Incidence Rates of Drug-Related Adverse Events Occurring in at Least 1% of Patients in Either Treatment Group Patients Valid for Safety

Adverse Event	Cipro XR (N=517)	Cipro BID (N=518)
Any Body System		
Any event	68 (13%)	70 (14%)
Body as a Whole		
Headache	7 (1%)	8 (2%)
Digestive		
Nausea	15 (3%)	15 (3%)
Diarrhea	12 (2%)	7 (1%)
Dyspepsia	7 (1%)	5 (<1%)
Vomiting	7 (1%)	4 (<1%)
Liver function tests abnormal	1 (<1%)	7 (1%)
Nervous		
Dizziness	9 (2%)	3 (<1%)
Urogenital		
Vaginal moniliasis	9 (2%)	7 (1%)

D. Adverse Events by Intensity

A small proportion of patients had events that were assessed by the investigator as severe in intensity. Seven percent (35/517) of all valid for safety patients in the Cipro XR group and 5% (28/518) in the Cipro BID group experienced at least one adverse event that was assessed by the investigator as severe in intensity. The type of severe adverse events by treatment group is shown in Table 52. The number of severe adverse events represents 14.6% (50/342) and 12.8% (39/304), respectively, of the total number of adverse events reported.

Reviewer's Comment: Table 52 was created by the reviewer.

TABLE 52
Number of Severe Adverse Events by Treatment Group in the Valid for Safety Population

	CIPRO XR	CIPRO 500 BID
ABDOMINAL PAIN	1	0
ABORTION	0	1
ACCIDENTAL INJURY	0	1
ACUTE KIDNEY FAILURE	1	1
ACUTE LEUKEMIA	0	1
ANEMIA	2	0
APNEA	1	0
ARTHRITIS	0	1
ASTHMA	1	1
BACK PAIN	1	1

	CIPRO XR	CIPRO 500 BID
BLADDER CARCINOMA	1	0
BODY AS A WHOLE SURGERY	1	0
CARCINOMA	1	2
CHEST PAIN	0	1
COLITIS	2	0
CONGESTIVE HEART FAILURE	2	0
CONSTIPATION	1	0
CORONARY ARTERY DISORDER	0	1
CYST (Baker's cyst, left knee)	1	0
DEEP THROMBOPHLEBITIS	0	1
DEHYDRATION	1	0
DIARRHEA	2	3
DIGESTIVE SURGERY	1	0
DIZZINESS	0	1
DYSPEPSIA	0	3
DYSPNEA	1	0
FEVER	0	1
FLANK PAIN	1	0
GASTROINTESTINAL DISORDER	1	0
GGTP INCREASED	0	1
GRANULOMA	1	0
HEADACHE	1	1
HEMATURIA	4	1
HEMORRHAGE	0	1
HYDRONEPHROSIS	1	0
HYPERTENSION	1	0
HYPERTONIA	0	1
HYPOVENTILATION	1	0
KIDNEY CALCULUS	3	0
KIDNEY FUNCTION ABNORMAL	0	1
KIDNEY PAIN	1	1
LARYNGEAL NEOPLASIA	1	0
LE SYNDROME (Systemic Lupus Erythematosus)	1	0
LEG PAIN	0	1
LIVER FUNCTION TESTS ABNORMAL	0	3
MYOCARDIAL INFARCT	0	1
NAUSEA	2	1
RECTAL HEMORRHAGE	0	1
SEPSIS	0	1
SMALL INTESTINE PERFORATION	0	1
STUPOR	1	0
URINARY RETENTION	4	0
URINARY TRACT INFECTION	1	1
UROGENITAL SURGERY	1	1
VOMITING	3	1
Total	50	39

E. Discontinuations

No action was taken as a result of more than 40% of all adverse events. A summary of the actions that were taken in response to adverse events is shown in Table 53. Except for a higher rate of study drug discontinuation in the Cipro XR group (i.e., 13.7% compared to 8.9% in the Cipro BID group), the distribution of actions taken for adverse events is similar overall between the two groups.

TABLE 53
Summary of Actions Taken for Adverse Events
Patients Valid for Safety

	Cipro XR 342 Adverse Events	Cipro BID 304 Adverse Events
None	140 (40.9%)	141 (46.4%)
Remedial drug therapy*	116 (33.9%)	97 (31.9%)
Discontinuation of study drug	47 (13.7%)	27 (8.9%)
Hospitalization	35 (10.2%)	30 (9.9%)
Other	47 (13.7%)	36 (11.8%)

Note: Number of actions taken for adverse events is greater than the number of adverse events because some events required more than one action.

*Remedial drug therapy = patient's treated with alternative antimicrobial(s)

A summary of the adverse events causing discontinuation of study drug are shown in Tables 54A and 54B.

Reviewer's Comment: Tables 54A and 54B were created by the reviewer.

Reviewer's Comment: The number of patient discontinuations due to an adverse event is higher in the Cipro XR group (5.4%; 28/517) compared to the Cipro BID group (3.7%; 19/324). The reviewer assessed the attributability of the adverse event to study drug, taking into account the patient's past medical history, the infection being treated, the temporal association of the event to initiation of the medication, and resolution of the event with discontinuation of the medication. In almost all instances, the reviewer's assessment (related or not related) corresponded with the investigator's assessment (possible/probable or unlikely/not related). The number of possible or probable events based on the investigator's assessment is 16/517 (3.1%) for Cipro XR and 12/518 (2.3%) for Cipro BID, which are considered similar.

TABLE 54A
Permanent Discontinuation of Study Medication Due to Adverse Event(s)
Cipro XR Treatment Group (N=28)
Patients Valid for Safety

Patient ID/Gender/ Age/Subgroup	Adverse Event(s) Leading to D/C	Study Drug Start Date/ End Date	Date of Onset of AE	Duration (Days)	Serious Adverse Event Criteria?	Relationship ^a
4001/F/79/cUTI	Urosepsis	8/1/01 – 8/2/01	8/3/01	6	Yes (hospitalization)	Not related
15006/M/20/cUTI	Bradycardia Dizziness Double Vision	10/10/01 – 10/11/01	10/11/01	2	No	Possible
			10/11/01	2	No	Possible
			10/11/01	2	No	Possible
18015/F/19/AUP	Gonorrhea	10/13/01 – 10/15/01	10/15/01	Unknown	No	Not related
29131/F/58/cUTI	Vomiting	5/1/02 – 5/1/02	5/1/02	1	No	Unlikely
29148/F/53/AUP	Bacteremia	6/28/01 – 6/29/01	6/28/01	2	Yes (hospitalization)	Not Related
48010/F/83/cUTI	Increased Diarrhea	9/18/01 – 9/22/01	9/18/01	2	No	Possible
41032/M/71/cUTI	Hypotension	11/16/01 – 11/17/01	11/17/01	1	Yes (hospitalization)	Unlikely
42047/F/42/cUTI	Stomach cramps Vomiting Chills	4/3/02 – 4/13/02	4/10/02	5	No	Possible
			4/10/02	4	No	Possible
			4/10/02	4	No	Unlikely
45013/F/78/cUTI	Lightheadedness Dizziness	9/28/01 – 9/29/01	9/29/01	2	No	Possible
			9/29/01	2	No	Possible
45039/F/67/cUTI	Stomach upset	2/26/02 – 3/1/02	2/26/02	4	No	Possible
48010/F/83/cUTI	Constipation	9/18/01 – 9/22/01	9/18/01	8	No	Possible
49002/F/83/cUTI	Upset Stomach	5/17/01 – 5/19/01	5/19/01	2	No	Probable
49010/F/72/cUTI	Faint Feeling	7/23/01 – 7/26/01	7/26/01	Unresolved	No	Possible
49014/F/90/cUTI	Elevated BUN, creatinine, uric acid, and amylase	8/8/01 – 8/10/01	8/8/01	Unresolved	No	Not related
50002/F/63/cUTI	Possible Sepsis	5/14/01 – 5/15/01	5/16/01	Unresolved	Yes (hospitalization)	Not related
50007/M/74/cUTI	Worsening urinary retention	10/9/01 – 10/16/01	10/16/01	Unresolved	No	Not related
62020/F/19/AUP	Worsening of vomiting	6/18/02 – 6/19/02	6/19/02	2	No	Possible
73035/F/32/cUTI	Headaches Lightheadedness Dizziness	1/25/02 – 1/29/02	1/25/02	6	No	Not related
73036/M/84/cUTI	Diarrhea Diverticulitis Stomach bloating Dizziness Lightheadedness Weakness Nightmares Worsening depression	2/7/02 – 2/10/02	2/9/02	30	No	Not related
			2/18/02	3	Yes (hosp)	Not related
			2/9/02	5	No	Not related
			2/9/02	5	No	Not related
			2/9/02	27	No	Possible
			2/9/02	27	No	Possible
			2/9/02	3	No	Probable
			2/9/02	1	No	Possible
77003/F/69/AUP	Fatigue	11/2/01 – 11/10/01	11/8/01	3	No	Probable
77011/F/84/cUTI	Worsening malaise	4/4/02 – 4/8/02	4/9/02	73	No	Possible

Patient ID/Gender/ Age/Subgroup	Adverse Event(s) Leading to D/C	Study Drug Start Date/ End Date	Date of Onset of AE	Duration (Days)	Serious Adverse Event Criteria?	Relationship ^a
82019/F/22/	Nausea Vomiting	11/28/01 – 12/1/01	11/29/01	3	No	Probable
			11/29/01	3	No	Probable
101002/M/90/cUTI	Headache Vertigo Nausea	3/6/02 – 3/7/02	3/7/02	2	No	Probable
			3/7/02	2	No	Probable
			3/7/02	2	No	Probable
101003/M/87/cUTI	Dizziness	3/6/02 – 3/8/02	3/8/02	Unresolved	No	Possible
137003/F/49/cUTI	Worsened kidney stones	4/29/02 – 5/1/02	5/1/02	1	No	Not related
211001/M/59/cUTI	Hematuria	1/30/02 – 2/4/02	1/31/02	Unresolved	No	Not related
211003/M/66/cUTI	Laryngeal tumor	2/11/02 – 2/12/02	2/12/02	Unresolved	Yes (hospitalization)	Not related
213001/M/56/AUP	Headache	1/16/02 – 1/20/02	1/19/02	2	No	Probable

D/C=discontinuation; M=male; F=female

^aRelationship as per the Investigator

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TABLE 54B
Permanent Discontinuation of Study Medication Due to Adverse Event(s)
Cipro BID Treatment Group (N=19)
Patients Valid for Safety

Patient ID/Gender/ Age/Subgroup	Adverse Event(s) Leading to D/C	Study Drug Start Date/ End Date	Date of Onset of AE	Duration (Days)	Serious Adverse Event Criteria?	Relationship ^a
6027/M/71/cUTI	Vomiting	5/31/02 – 6/8/02	6/4/02	7	No	Possible
18004/M/30/AUP	Elevated AST Elevated ALT	8/24/01 – 8/30/01	8/27/01 8/27/01	12 12	No No	Possible Possible
19016/F/57/cUTI	Diarrhea	5/21/02 – 5/23/02	5/22/02	2	No	Probable
20006/F/21/cUTI	Nausea	8/30/01 – 9/1/01	8/30/01	3	No	Possible
49012/F/59/cUTI	Elevated LFTs	7/27/01 – 8/1/01	7/30/01	Unresolved	No	Probable
49016/F/75/cUTI	Headache	8/10/01 – 8/10/01	8/10/01	2	No	Possible
59019/M/21/cUTI	Abdominal cramping	1/17/02 – 1/22/02	1/18/02	Unresolved	No	Probable
59026/F/79/cUTI	Nausea Diarrhea	2/14/02 – 2/18/02	2/18/02 2/18/02	2 1	No	Possible Possible
62006/F/47/AUP	Itching	10/13/01 – 10/23/01	10/22/01	5	No	Probable
68004/F/54/cUTI	Worsening vaginal yeast infection	10/31/01 – 11/5/01	10/31/01	Unresolved	No	Not related
73037/M/82/cUTI	Musculoskeletal chest pain	2/7/02 – 2/8/02	2/8/02	3	No	Not related
74015/M/66/cUTI	Elevated LFTs	6/14/02 – 6/19/02	6/17/02	Unresolved	No	Possible
89001/F/84/cUTI	Elevated LFTs	11/13/01 – 11/19/01	11/16/01	37	No	Probable
90014/M/93/cUTI	Chest Pain	8/24/01 – 8/26/01	9/14/01	2	Yes (hosp)	Not related
90077/M/91/cUTI	Worsening dehydration	11/2/01 – 11/9/01	11/6/01	14	No	Unlikely
118054/F/18/AUP	Persistent tachycardia Persistent hypotension	5/2/02 – 5/2/02	2/2/02 5/2/02	16 16	Yes (hosp) Yes (hosp)	Not related Not related
125001/F/69/cUTI	Worsening dyspnea (intermittent) Leg weakness Increased anxiety	3/18/02 – 3/20/02	3/19/02 3/19/02 3/19/02	2 2 2	No No No	Not related Not related Not related
142007/F/77/cUTI	Muscle pain right arm Muscle pain left arm	4/12/02 – 4/17/02	4/12/02 4/12/02	10 29	No No	Unlikely Unlikely
213006/M/41/AUP	Vomiting	4/17/02 – 4/17/02	4/18/02	2	No	Possible

D/C=discontinuation; M=male; F=female

^aRelationship as per the Investigator

F. Deaths

Three patients in the Cipro XR group and one patient in the Cipro BID group died during the study period or during the follow-up period as shown in Table 55. All four patients had an underlying diagnosis of cUTI with one underlying condition (indwelling urinary catheter, 100 mL residual urine after voiding, or urinary retention due to benign prostatic hypertrophy). In the Cipro XR group, one of the deaths occurred 35 days after the end of study drug treatment, another occurred

during treatment, and in the third case the date of the last dose was unknown. The patient death in the Cipro BID group occurred 97 days after the end of the treatment. In all cases, the serious adverse event resulting in death was judged by the investigator to be unlikely or not related to study drug therapy, and the cause of death was reported as a concomitant condition.

TABLE 55
Summary of Patient Deaths

Treatment Group	Patient Number	Sex/Age (yr)	Day of Death Relative to		Event with Outcome of Death	Cause of Death
			First Dose	Last Dose		
Cipro XR	49015	M/95	17	unknown	Acute renal failure	Renal failure
Cipro XR	52008	F/89	43	35	Respiratory failure	Respiratory failure
Cipro XR	52012	M/76	8	0	Worsening of congestive heart failure (CHF)	Sudden death probably due to worsening of CHF
Cipro BID	73037	M/82	99	97	Left renal cancer with metastasis	Renal cell carcinoma

A short narrative of each patient who died is included below:

Patient 49015

This 95-year-old Caucasian man was enrolled for the treatment of cUTI with an indwelling urinary catheter. His medical history consisted of: hypertension, angina pectoris, constipation, back pain, seizure, prostate cancer, transurethral resection of the prostate, urinary retention, bladder outlet obstruction, hot flashes, indwelling urinary catheter, arteriosclerotic cardiovascular disease, and cerebrovascular accident. Concomitant medications included Lupron (leuprolide), Dilantin (phenytoin), enalapril, Vioxx (rofecoxib), Ditropan XL (oxybutynin), nitroglycerin, Darvocet-N (acetaminophen and propoxyphene), Lasix (furosemide), albuterol, Atrovent (ipratropium bromide), and morphine sulfate.

Ten days after his initial dose of study drug therapy, he was hospitalized with severe hematuria and acute renal failure. His creatinine values were 1 mg/dL at pretreatment (normal 0.5 - 1.6 mg/dL) and 1.2 mg/dL during treatment. His BUN values were 24 mg/dL at pretreatment (normal 4 - 34 mg/dL) and 25 mg/dL during treatment. Values for these two laboratory tests were unknown at the time of death. No treatment was reported for acute renal failure. He also had pulmonary edema, which was treated with Lasix (furosemide), and shortness of breath, which was treated with albuterol and Atrovent (ipratropium bromide).

Other events reported over the next 6 days were wheezing, bilateral ureteral obstruction, left atrial enlargement, right ventricular hypertrophy, bilateral hydronephrosis, bilateral renal cysts, swollen and discolored left hand, cardiomegaly, and anemia, (hemoglobin on Day 1 was 11.2 g/dL; 4 days later it was 10.7 g/dL [normal range is 12.5-17 g/dL]). No action was taken for these events, all of which remained unchanged except the acute renal failure, which resulted in his death on 7 days following hospitalization.

The investigator found it unlikely there was any relationship between the study drug and events of hematuria, shortness of breath, renal failure, pulmonary edema, hydronephrosis, renal cysts, anemia, and wheezing. The swollen and discolored hand, cardiomegaly, atrial enlargement, ventricular hypertrophy, and ureteral obstruction were all considered unrelated to the study drug. The patient died 17 days after the start of study drug. It could not be determined when the patient took his last dose. Death was reportedly due to acute renal failure. The investigator found it unlikely there was any relationship between the study drug and the patient's death.

Patient 52008

This 89-year-old Caucasian woman was enrolled for the treatment of a cUTI with an indwelling urinary catheter. Her medical history consisted of hypertension, degenerative joint disease, diverticulosis, congestive heart failure, gastroesophageal reflux disease, angina pectoris, arteriosclerotic cardiovascular disease, depression, organic brain syndrome, post-menopausal, hysterectomy, and constipation. Concomitant medications included Lasix (furosemide), Norvasc (amlodipine), Lopressor (metoprolol), aspirin, Celexa (citalopram), Vioxx (rofecoxib), Surfak (docusate calcium), Isordil (isosorbide), Prevacid (lansoprazole), and Duragesic (fentanyl) patch. Thirty-four days after her last dose of study drug, she experienced respiratory failure due to congestive heart failure and general debilitation. Since she was on "do not resuscitate" orders by her family, the only treatment she received was palliative and she died of respiratory failure one day later. Her respiratory failure was considered not related to study drug.

Patient 52012

This 76-year-old Caucasian man was enrolled for the treatment of a cUTI with 100 mL of residual urine after voiding. His medical history consisted of myocardial infarction, congestive heart failure, atrial fibrillation, coronary artery disease, aortic stenosis, cardiomyopathy, COPD, respiratory failure, cardiac shock, pacemaker, coronary artery bypass surgery, prosthetic aortic valve, transurethral resection, bladder tumor, torn left rotator cuff repair, hyperglycemia, left bundle branch block, coronary stents, malfunction of prosthetic aortic valve and angina pectoris. Concomitant medications included Coumadin (warfarin), Lasix (furosemide), Coreg (carvedilol), Lanoxin (digoxin), aspirin, Cordarone (amiodarone) and Combivent inhaler (ipratropium/albuterol). On the 5th day of the study, his congestive heart failure worsened and he received remedial treatment with Lasix. He died 3 days later (8 days after beginning study drug therapy). Although the death certificate listed the cause of his death as "natural causes", the investigator believed his congestive heart failure was the actual cause of his death. The patient took his last dose of study medication approximately 6 p.m. on [redacted]. The patient went to bed at approximately 10 p.m., and at about 11 p.m. the patient's spouse noted that he was non-responsive and called an ambulance. The patient was declared dead at 12:40 a.m. on [redacted]. The investigator considered the event unrelated to the study drug.

Patient 73037

This 82-year-old Caucasian man was enrolled for treatment of a cUTI secondary to urinary retention due to BPH. His medical history consisted of shingles,

bilateral lens implant, bilateral laser eye surgery, BPH, hepatitis A, hypercholesterolemia, hypertension, and bilateral cataracts. His concomitant medications included Lipitor (atorvastatin), aspirin, Metamucil (psyllium), droperidol, potassium chloride, Dulcolax (bisacodyl), propofol, fentanyl, sevoflurane, Versed (midazolam), Zemuron (rocuronium), Robinul (glycopyrrolate), and neostigmine. This patient entered the study with blood in his urine secondary to the complicated urinary tract infection under study. The patient's pre-therapy LDH value was 285 U/L (normal range: 53 – 234 U/L); however, this was considered "not clinically significant" by the investigator. A repeat LDH value on Day 5 was still 285 U/L. On the 2nd day of study drug therapy, he developed musculoskeletal chest pain and the study drug was permanently discontinued. The following day, he had worsening of blood in his urine; no action was taken for this event. Both events resolved the next day and neither were considered related to study drug. The patient was given Septra DS (trimethoprim/sulfamethoxazole) as alternative therapy the day after study drug was discontinued to complete the course of therapy for his UTI. The 3rd day after the last dose of study drug, he was diagnosed with left renal cancer with metastasis and was hospitalized 5 days later to undergo left radical nephrectomy and periaortic lymphadenopathy. He did well following surgery and was discharged from the hospital two days later. The patient died 97 days following the completion of study drug therapy. The cause of death was metastatic renal cell carcinoma and it was not considered to be related to study drug.

G. Non-fatal Serious Adverse Events

Five percent (5%) of patients in both treatment groups experienced non-fatal serious adverse events (SAEs) (28/517 and 24/518, respectively). A summary of the non-fatal SAEs are shown in Tables 56A and 56B.

Reviewer's Comment: Tables 56A and 56B were created by the reviewer.

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TABLE 56A
Listing of Patients with Non-Fatal Serious Adverse Events (SAEs)
Cipro XR Treatment Group (N=28)
Patients Valid for Safety

Patient ID/Gender/ Age/Subgroup	SAE(s)	Study Drug Start Date/ End Date	Date of Onset of SAE	Duration of SAE (Days)	SAE Criteria	Relationship ^a
4001/F/79/cUTI	Urosepsis	8/1/01 – 8/2/01		7	Hospitalization	Not related
6026/M/78/cUTI	Hemoptysis	3/22/02 – 4/3/02	[]	8	Hospitalization	Not related
	Transient Hypotension			1	Hospitalization	Not related
	Pneumonia			8	Hospitalization	Not related
12005/M/68/cUTI	Unstable angina	2/27/02 – 3/12/02		4	Hospitalization	Not related
13001/F/36/AUP	Cellulitis, right hand	5/21/01 – 6/3/01		2	Hospitalization	Not related
15014/F/19/cUTI	Sickle cell crisis	1/21/02 – 1/28/02		5	Hospitalization	Not related
	Sickle cell crisis			2	Hospitalization	Not related
27010/M/81/cUTI	Worsening Hypertension	2/5/02 – 2/14/02		3	Hospitalization	Not related
29148/F/53/AUP	Bacteremia	6/28/02 – 6/29/02		2	Hospitalization	Not related
41031/M/77/cUTI	Elective Transurethral Prostatic Resection	11/16/01 – 11/29/01		1	Hospitalization	Not related
41032/M/71/cUTI	Hypotension	11/16/01 – 11/17/01		1	Hospitalization	Unlikely
42029/M/91/cUTI	Blood clot in Foley catheter	12/07/01 – 12/20/01		2	Hospitalization	Not related
42056/F/53/cUTI	Recurrent Pericardial Effusion	6/7/02 – 6/20/02		5	Hospitalization	Not related
45022/M/56/cUTI	Transitional cell carcinoma of bladder	11/16/02 - unknown		Unresolved	Life-threatening medical event	Not related
49015/M/95/cUTI	Hematuria Acute Renal Failure	[] - unknown		Unresolved 7	Hospitalization Hospitalization, Death	Unlikely Unlikely
50002/F/63/cUTI	Possible sepsis	5/14/01 – 5/15/01		Unresolved	Hospitalization	Not related
52004/F/81/cUTI	Rectal bleeding Worsening of hemorrhoids	10/11/01 – 10/17/01		9	Hospitalization	Not related
				9	Hospitalization	Not related
52008/F/89/cUTI	Respiratory Failure (due to congestive heart failure)	[]		2	Death	Not related
52012/M/76/cUTI	Worsening of congestive heart failure	[]		4	Death	Not related
53024/F/54/cUTI	Unresponsiveness Hypoventilation	1/8/02 – 1/22/02		2	Hospitalization	Not related
				2	Hospitalization	Not related
53026/F/62/cUTI	Exacerbation of systemic lupus erythematosus	1/9/02 – 1/25/02		5	Hospitalization	Not related
59014/F/74/cUTI	Exacerbation of congestive heart failure	1/4/02 – 1/4/02		4	Hospitalization	Not related
63001/F/55/cUTI	Recurrent UTI	4/19/01 – 5/2/01		4	Hospitalization	Not related
63016/M/41/cUTI	Dehydration	9/17/01 – 9/30/01		3	Hospitalization	Unlikely
73036/M/84/cUTI	Diverticulitis	2/7/02 – 2/10/02	[]	3	Hospitalization	Not related

Patient ID/Gender/ Age/Subgroup	SAE(s)	Study Drug Start Date/ End Date	Date of Onset of SAE	Duration of SAE (Days)	SAE Criteria	Relationship ^a
74012/M/52/AUP	Right renal carcinoma Calcified sclerotic granuloma in lungs	3/18/02 – 3/31/02	✓	1	Hospitalization	Not related
				1	Hospitalization	Not related
97002/M/78/cUTI	Chest pains	8/7/01 – 8/18/01		2	Hospitalization	Unlikely
102014/F/73/cUTI	Colo-vesical fistula Diverticulosis Colonic resection Surface ulceration of colon	2/20/02 – 3/1/02		2	Hospitalization	Not related
				Unresolved	Hospitalization	Not related
				1	Hospitalization	Not related
				1	Hospitalization	Not related
148007/F/77/cUTI	Breast cancer Abdominal pain	4/18/02 – 5/1/02	└	Unresolved 9	Hospitalization Hospitalization	Not related Not related
211003/M/66/cUTI	Laryngeal tumor	2/11/02 – 2/12/02		Unresolved	Hospitalization	Not related

^a Relationship as per the Investigator.

Reviewer's Comment: Among the three patients in the Cipro XR treatment group for whom a serious adverse event of sepsis was reported, 2 (4001 and 50002) had negative blood culture results and one (29148) had positive blood culture results for E. coli. Repeat blood culture results on the following day for this latter patient were negative, and furthermore, although study drug was discontinued, the alternative antimicrobial administered was ciprofloxacin. One (73007) of the two patients in the Cipro BID treatment group had a positive pretreatment blood culture result for E. coli, continued treatment with Cipro BID, and the event resolved. The other patient (74015) with reported sepsis in the Cipro BID group developed presumed septicemia while on alternative antimicrobial therapy (cinnoxacin) and no blood culture specimens were obtained.

Of the two patients in the Cipro XR treatment group with a reported serious adverse event of hypotension, one (6026) had transient hypotension detected on hospital admission for other adverse events and the other (41032) was receiving triple-drug antihypertensive therapy. In the former case, study drug therapy was not discontinued; in the latter case, study drug therapy was discontinued but alternative therapy was instituted with commercially available ciprofloxacin.

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TABLE 56B
Listing of Patients with Non-Fatal Serious Adverse Events
Cipro BID Treatment Group (N=24)
Patients Valid for Safety

Patient ID/Gender/ Age/Subgroup	SAE(s)	Study Drug Start Date/ End Date	Date of Onset of SAE	Duration (Days)	SAE Criteria	Relationship ^a
17004/F/71/cUTI	Right hip arthroplasty	8/7/01 – 8/21/01	[10	Hospitalization	Not related
19010/M/63/AUP	Lung surgery	9/10/01 – 9/16/01		6	Hospitalization	Not related
25011/F/69/cUTI	Rectal bleeding	8/27/01 – 9/9/01		4	Hospitalization	Not related
	Rectal polyps			1	Hospitalization	Not related
40003/M/74/cUTI	Acute lymphocytic leukemia	8/10/01 – 8/23/01		Unresolved	Life-threatening event	Not related
41018/M/68/cUTI	Transurethral prostatectomy	10/12/01 – 10/18/01		2	Hospitalization	Not related
45036/F/83/cUTI	Worsening of angina Stenosis of right coronary artery Worsening of coronary artery disease	2/8/02 – 2/14/02		7	Hospitalization	Not related
				7	Hospitalization	Not related
				7	Hospitalization	Not related
52006/F/78/cUTI	Acute renal failure	10/17/01 – 10/22/01		5	Hospitalization	Not related
53021/M/83/cUTI	Urinary bladder stones	10/30/01 – 11/13/01		10 Unresolved	Hospitalization	Not related
	Adenocarcinoma of the bladder				Hospitalization	Not related
59005/M/64/cUTI	Musculoskeletal back spasms	8/6/01 – 8/19/01		2	Hospitalization	Not related
59010/F/69/cUTI	Myocardial infarction Angina pectoris	11/2/01 – 11/15/01		4 Unresolved	Hospitalization	Not related
					Hospitalization	Not related
73007/F/73/AUP	Urosepsis	4/30/01 – 5/13/01		19	Prolongation of Hospitalization	Not related
73009/F/72/cUTI	Right coronary artery occlusion	5/7/01 – 5/7/01		2	Hospitalization	Not related
73019/M/88/cUTI	Coronary artery disease Excessive post-op bleeding Bronchospasm	7/20/01 – 7/26/01		Unresolved 1 1	Hospitalization	Not related
					Hospitalization	Not related
					Hospitalization	Not related
73037/M/82/cUTI	Left renal cancer with metastasis	[]	Unresolved	Death	Not related
74015/M/66/cUTI	Elevated temperature Septicemia	6/14/02 – 6/19/02		6 6	Hospitalization	Not related
					Hospitalization	Not related
82011/F/72/AUP	Abdominal pain	10/9/01 – 10/9/01		2	Hospitalization	Not related
82025/F/34/AUP	Perforated duodenum secondary to duodenal ulcer repair	12/19/01 – 12/29/01		8	Hospitalization	Unlikely
82028/F/42/AUP	Deep vein thrombosis	1/26/02 – 2/6/02		2	Hospitalization	Not related
90014/M/93/cUTI	Chest pain	8/24/01 – 8/26/01		2	Hospitalization	Not related
95017/F/71/cUTI	Vomiting	9/25/01 – 10/8/01		7	Hospitalization	Not related
118054/F/18/AUP	Persistent tachycardia Persistent hypotension	5/2/02 – 5/2/02		15 15	Hospitalization	Not related
					Hospitalization	Not related
123003/M/67/cUTI	Bleeding internal hemorrhoid	3/15/02 – 3/29/02	U	3	Hospitalization	Not related

Patient ID/Gender/ Age/Subgroup	SAE(s)	Study Drug Start Date/ End Date	Date of Onset of SAE	Duration (Days)	SAE Criteria	Relationship ^a
142015/M/84/cUTI	Pneumonia	5/15/02 – 5/28/02	[]	5	Hospitalization	Unlikely

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Patient ID/Gender/ Age/Subgroup	SAE(s)	Study Drug Start Date/ End Date	Date of Onset of SAE	Duration (Days)	SAE Criteria	Relationship ^a
149006/M/48/cUTI	Worsening of kidney pain	[] - unknown	[]	1	Significant disability/ incapacity (outpatient surgical intervention)	Not related

^a Relationship as per the Investigator.

Reviewer's Comment: The patient (118054) in the Cipro BID group for whom hypotension was reported as a serious adverse event (SAE) had a history of hypotension. Hypotension (blood pressure of 92/52 mmHg) was reported as a SAE on the first day of study drug treatment, study drug was prematurely discontinued, and alternative therapy included a dose of ceftriaxone followed by ciprofloxacin. The hypotension resolved.

H. Pregnancy

One pregnancy was reported during the study in a patient treated with Cipro BID.

Patient 31042

This 19-year-old woman was enrolled for the treatment of AUP. Concomitant medication included Ortho-Cyclen (norgestimate/ethinyl estradiol). On the 11th day of the study she experienced nausea and lightheadedness for which no action was taken. Twenty-three (23) days after her final dose of study medication, she discovered she was pregnant and elected to terminate the pregnancy 15 days later; a telephone follow-up 1 month later revealed no sequelae to the procedure. All adverse events resolved. The nausea and lightheadedness were considered possibly related to the study drug; the unintended pregnancy was considered not related.

I. Evaluation of Laboratory Parameters

Laboratory variables that showed at least a 2% incidence rate of abnormalities in at least one of the treatment groups are shown in Table 57. The incidence of abnormal laboratory test results is low and generally consistent between the two treatment groups.

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TABLE 57
Incidence Rates^a of Laboratory Abnormalities Occurring in at least
2% of Patients in Either Treatment Group
Patients Valid for Safety

Laboratory Variable ^b	Cipro XR	Cipro BID
High		
WBC	14/365 (4%)	23/356 (6%)
Neutrophils (segs) absolute count	28/358 (8%)	20/336 (6%)
Lymphocytes absolute count	17/448 (4%)	10/452 (2%)
Eosinophils absolute count	8/464 (2%)	4/465 (<1%)
Platelets	31/421 (7%)	34/426 (8%)
PT ^c	4/55 (7%)	3/55 (5%)
Glucose, fed, unspecified ^d	0/52 (0%)	4/48 (8%)
Uric acid	23/436 (5%)	29/442 (7%)
Creatinine	22/435 (5%)	19/443 (4%)
BUN	17/442 (4%)	19/456 (4%)
SGOT/AST	22/434 (5%)	27/424 (6%)
SGPT/ALT	33/432 (8%)	27/426 (6%)
GGT	13/416 (3%)	16/400 (4%)
LDH	12/434 (3%)	17/441 (4%)
Alkaline phosphatase	7/450 (2%)	12/455 (3%)
Bilirubin, total	6/458 (1%)	8/469 (2%)
Amylase	26/411 (6%)	39/414 (9%)
Specific gravity	16/460 (3%)	11/468 (2%)
Low		
Hematocrit	42/412 (10%)	25/419 (6%)
Hemoglobin	41/392 (10%)	27/408 (7%)
WBC	10/464 (2%)	11/467 (2%)
Neutrophils (segs) absolute count	12/464 (3%)	14/469 (3%)
Lymphocytes absolute count	13/447 (3%)	10/449 (2%)
Bilirubin, total	30/445 (7%)	30/462 (6%)
Specific gravity	52/440 (12%)	53/460 (12%)

^a Incidence rate = Number of patients with the abnormality after pretreatment / Number of patients with readings during and after pretreatment who did not have the abnormality during pretreatment.

^b Fasting state was not mandated.

^c Samples for PT were obtained only from patients who were receiving concomitant therapy with Coumadin.

^d Glucose, fed or unspecified; values for this laboratory analyte (n = 100 patients) were determined only after approval of Protocol Amendment # 6.

The incidence rates of urine abnormalities are similar between the two treatment groups. Blood was documented in urine macroscopically in about one-fifth of patients (20% in Cipro XR patients and 17% in Cipro BID patients). RBCs are seen in the urine in 14% and 17% of patients treated with Cipro XR and Cipro BID, respectively. Hematuria was reported as an adverse event in < 1% of patients in either treatment group (5 Cipro XR patients and 3 Cipro BID patients), of which only 1 case (Cipro XR, Patient 142021) was considered by the investigator to be drug related. This patient, was receiving warfarin for atrial

fibrillation and presented at study entry with moderate hematuria among other signs and symptoms of cUTI, developed gross hematuria one day after starting Cipro XR therapy. His INR the following day was 1.98. The event resolved in one day without any intervention. The patient had no other adverse events.

Changes from baseline for all laboratory variables generally are comparable between the two treatment groups. Of the 5 patients who discontinued study drug therapy prematurely due to laboratory test abnormalities (Patient 49014 in the Cipro XR group with elevated BUN and creatinine and Patients 18004, 49012, 74015 and 89001 in the Cipro BID group with increased liver function tests), four had elevations at baseline. The fifth patient, an 84 year of female (Patient 89001) in the Cipro BID group, experienced an increase in liver enzymes (SGOT/AST, SGPT/ALT, GGT, LDH, and alkaline phosphatase) and total bilirubin during the study. The laboratory values are well within the normal range at baseline but increased from 1.5- to >10-times the upper limit of normal three days after beginning study drug. The patient did not experience jaundice, nausea or vomiting during the time of elevated tests. Study drug was discontinued and the tests all returned to baseline and are in the normal range by 18 days following the discontinuation of study drug.

Criteria used to define potentially clinically significant changes for common laboratory variables are as follows: < 75% of the lower limit of normal for hemoglobin; <100,000/mm³ for platelets; > 0.5 mg/dL and > 1mg/dL increase from baseline for serum creatinine; ≥ 1.8 and > 3 times the upper limit of normal (ULN) for SGPT (ALT), SGOT (AST) and total bilirubin; and < 50 mg/dL for serum glucose. The highest incidence of such changes in the Cipro XR group is 2% for creatinine increase > 0.5 mg/dL from baseline, SGOT/AST, and SGPT/ALT >1.8 times ULN as shown in Table 58. In the Cipro BID group the highest incidence of clinically significant changes also is 2% for elevation of liver enzymes (SGOT/AST, and SGPT/ALT) > 1.8 and > 3 times ULN.

TABLE 58
Incidence of Clinically Significant Laboratory Abnormalities
Patients Valid for Safety

Variable	Criterion	Cipro XR		Cipro BID	
		n/n	%	n/n	%
Hemoglobin	0.75 x lower limit or less	2/479	<1	1/481	<1
Total bilirubin	≥1.8 x ULN	2/484	<1	2/491	<1
	≥3 x ULN	1/484	<1	1/493	<1
Creatinine	Increase of 0.5 mg/dL from baseline	11/486	2	6/498	1
	Increase of 1 mg/dL from baseline	3/486	1	1/498	<1
SGOT/AST	≥1.8 x ULN	8/464	2	11/467	2
	>3 x ULN	4/472	1	8/477	2
SGPT/ALT	≥1.8 x ULN	9/475	2	10/467	2
	>3 x ULN	6/479	1	10/481	2

Of the three patients with hemoglobin values <75% of the lower limit of normal, only one patient (Cipro BID, Patient 90014) had symptoms that could potentially

be associated with anemia (chest pain, malaise, and worsening of shortness of breath). However, considering the timing of adverse events, malaise is more likely to have been a consequence of indigestion and diarrhea that the patient developed at the same time. This patient also had a history of anemia and shortness of breath as well as multiple cardiovascular conditions, including aortic stenosis, congestive heart failure, angina pectoris, arteriosclerosis, hypertension, to which the other two adverse events could have been related.

Reviewer's Comment: Two patients had clinically significant increases ($\geq 3 \times$ ULN; ULN = 1.2 mg/dL) in total bilirubin after receiving study drug. Patient 95009 was a 57-year-old Caucasian female randomized to Cipro BID for cUTI. Her pre-test total bilirubin was 0.7 mg/dL, which increased to 6 mg/dL at the TOC visit. However at the post-therapy visit the value was decreased to 0.2 mg/dL. There was no concurrent increase in AST or ALT with the rise in total bilirubin at the TOC visit.

Patient 124004 was an 82-year-old Caucasian female randomized to Cipro XR for cUTI. Her pre-test total bilirubin was 0.6 mg/dL. At the during therapy visit, the value increased to 1.1 mg/dL, and was noted to be 4.8 mg/dL at the TOC visit. An additional visit, scheduled more than one month after the end of therapy, showed a reduction in total bilirubin to 1.3 mg/dL. The values of AST and ALT remained within normal limits throughout.

Although there are more patients in the Cipro XR group whose creatinine levels rose from baseline by more than 0.5 mg/dL (11 versus 6 patients), comparable numbers of patients in both treatment groups had a change in creatinine levels from baseline greater than 1 mg/dL (3 versus 1 patient). For only one of these patients (Cipro XR, Patient 82019) the increase in creatinine level (from 0.8 mg/dL at baseline to 2.8 and 3.0 mg/dL on the third and fourth days of study drug therapy, respectively) was reported as an adverse event and the patient developed possibly related symptoms of nausea, vomiting, and tingling in extremities. The event resolved in about 1 month (creatinine levels were 2.1, 1.7, and 0.9 mg/dL on the second, fifth, and thirty-fourth post-treatment days, respectively). Only 1 patient (Cipro XR, 49014) discontinued study drug due to abnormal kidney function, which was detected at baseline (creatinine 2.3 mg/dL pre-treatment; 2.5 mg/dL on Day 3; 2.5 mg/dL at +7 days post-treatment; and BUN 91 mg/dL pretreatment; 96 mg/dL on Day 3; 99 mg/dL at +7 days post-treatment).

In the two treatment groups, the incidence of clinically significant ($>1.8 \times$ ULN) abnormalities in SGOT and SGPT is the same (2%). For abnormalities in SGOT and SGPT that were $>3 \times$ ULN, the incidence is 1% in the Cipro XR group and 2% in the Cipro BID group. Two patients ($<1\%$) in the Cipro XR group had liver function test abnormalities that were reported as adverse events. For one patient (31035) the liver enzyme levels were increased less than $1.8 \times$ ULN and were thought to be possibly related to study drug. In the other patient (25008) the liver enzyme levels were $3 \times$ ULN and $4.8 \times$ ULN for SGOT and SGPT, respectively, and not believed to be related to study drug. In both cases, the events resolved and did not require discontinuation of study drug.

Seven patients (1%) treated with Cipro BID had abnormal liver function test results that were reported as adverse events. In 4 of these 7 patients, the liver function test abnormalities were a reason for discontinuation of study medication. Only one patient (89001) of the 4 patients in the Cipro BID group who discontinued prematurely for liver function test abnormalities had all tests within the normal range at baseline. This patient had diabetes mellitus and was receiving concomitant therapy with oral antidiabetic agents and insulin. On Day 4, her SGOT and SGPT levels increased to >10 x ULN, GGT to >5 x ULN, LDH to >2 x ULN, alkaline phosphatase to 1.4 x ULN, and total bilirubin to 3 x ULN. Values returned toward baseline levels following discontinuation of study drug, and the investigator judged the event of elevated liver function tests to be probably study related.

J. Vital signs, physical findings, and other observations related to safety

All vital signs are comparable between the two treatment groups throughout the study (i.e., pre-therapy, test of cure, and follow-up). The mean change from pre-therapy at the TOC visit and at the late follow-up visit for all vital signs variables generally are minimal (data not shown).

XI. Safety Results for Special Populations

A. Age

Adverse events occurring in at least 2% of patients in any age group (< 65 years, 65 to 74 years and ≥ 75 years) are summarized in Table 59.

The overall incidence rates of adverse events are similar across age groups (< 65 years, 65-74 years, and ≥ 75 years) in patients within each treatment group. For both the Cipro XR and Cipro BID group, patients aged 65-74 years experienced nausea less frequently than those younger or older. More patients younger than 65 years of age in the Cipro XR group reported vomiting [4% (12/271)] than did patients in the same age category treated with Cipro BID [<1% (2/255)]. The incidence of dizziness in patients 75 years of age or older is slightly higher in the Cipro XR group [4% (6/149)] as compared to the Cipro BID group [1% (2/159)]. The incidence rates of other adverse events for both treatment groups across age groups are similar.

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TABLE 59
Incidence Rates of Adverse Events by Age
Occurring in at least 2% of Any Age Group by Treatment Group
Patients Valid for Safety

Adverse Event	n (%)					
	<65 Years		65-74 Years		≥ 75 Years	
	Cipro XR N = 271	Cipro BID N = 255	Cipro XR N = 97	Cipro BID N = 104	Cipro XR N = 149	Cipro BID N = 159
Any Body System						
Any Event	85 (31)	79 (31)	29 (30)	36 (35)	51 (34)	50 (31)
Body as a Whole						
Any Event	31 (11)	32 (13)	5 (5)	10 (10)	18 (12)	16 (10)
Headache	12 (4)	14 (5)	0 (0)	4 (4)	5 (3)	7 (4)
Abdominal pain	2 (<1)	0 (0)	1 (1)	0 (0)	3 (2)	0 (0)
Back pain	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	3 (2)
Fever	0 (0)	3 (1)	0 (0)	2 (2)	0 (0)	1 (<1)
Asthenia	0 (0)	0 (0)	3 (3)	0 (0)	1 (<1)	0 (0)
Sepsis	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Cardiovascular System						
Any Event	4 (1)	6 (2)	9 (9)	3 (3)	7 (5)	7 (4)
Peripheral edema	1 (<1)	0 (0)	2 (2)	0 (0)	2 (1)	0 (0)
Hypotension	0 (0)	0 (0)	2 (2)	0 (0)	1 (<1)	0 (0)
Digestive System						
Any Event	41 (15)	32 (13)	7 (7)	16 (15)	23 (15)	19 (12)
Nausea	14 (5)	11 (4)	1 (1)	2 (2)	9 (6)	10 (6)
Diarrhea	8 (3)	6 (2)	0 (0)	1 (<1)	7 (5)	4 (3)
Vomiting	12 (4)	2 (<1)	1 (1)	3 (3)	1 (<1)	3 (2)
Dyspepsia	5 (2)	2 (<1)	3 (3)	1 (<1)	1 (<1)	3 (2)
Constipation	2 (<1)	3 (1)	0 (0)	3 (3)	3 (2)	3 (2)
LFTs abnormal	0 (0)	3 (1)	0 (0)	2 (2)	0 (0)	2 (1)
Rectal hemorrhage	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
GI neoplasia	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Nervous System						
Any Event	14 (5)	8 (3)	4 (4)	8 (8)	12 (8)	4 (3)
Dizziness	6 (2)	3 (1)	4 (4)	5 (5)	6 (4)	2 (1)
Anxiety	0 (0)	1 (<1)	0 (0)	2 (2)	0 (0)	0 (0)
Respiratory System						
Any Event	9 (3)	14 (5)	6 (6)	3 (3)	4 (3)	4 (3)
Pharyngitis	2 (<1)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)
Skin and Appendages						
Any Event	7 (3)	4 (2)	1 (1)	0 (0)	2 (1)	6 (4)
Pruritus	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	3 (2)

Adverse Event	n (%)					
	<65 Years		65-74 Years		≥ 75 Years	
	Cipro XR N = 271	Cipro BID N = 255	Cipro XR N = 97	Cipro BID N = 104	Cipro XR N = 149	Cipro BID N = 159
Urogenital System						
Any Event	20 (7)	20 (8)	5 (5)	5 (5)	14 (9)	9 (6)
Vaginal moniliasis	7 (3)	7 (3)	2 (2)	0 (0)	1 (<1)	1 (<1)
Urinary retention	2 (<1)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)
Hematuria	1 (<1)	0 (0)	0 (0)	0 (0)	4 (3)	0 (0)

Note: Incidence rate = Number of events / Number of patients, where number of events is the number of patients reporting the event with a start date during or after treatment

Reviewer's Comment: The differences seen in adverse events between younger and older patients treated with Cipro XR are not considered clinically meaningful and do not warrant reporting by age in product labeling.

B. Sex

Adverse events occurring in at least 2% of patients in any treatment group by sex are shown in Table 60.

Within each sex, the event rates are similar between Cipro XR and Cipro BID patients. Overall, female patients have higher event rates than male patients [34% (102/298) for females vs. 29% (102/299) for males]. Overall, female patients have higher rates of nausea and diarrhea [nausea: 6% in both Cipro XR (19/298) and Cipro BID (18/299) groups; diarrhea: 4% (11/298) in Cipro XR and 3% (8/299) in Cipro BID] than the male patients [nausea: 2% in both Cipro XR (5/219) and Cipro BID (5/219) groups; diarrhea: 2% (4/219) in Cipro XR and 1% (3/219) in Cipro BID]. Of the Cipro XR treated patients more females reported vomiting [4% (12/298)] than males [<1% (2/219)].

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TABLE 60
Incidence Rates of Adverse Events by Sex
Occurring in at least 2% of Patients of Either Sex
Patients Valid for Safety

Adverse Event	n (%)			
	Male		Female	
	Cipro XR N=219	Cipro BID N=219	Cipro XR N=298	Cipro BID N=299
Any Event	63 (29%)	63 (29%)	102 (34%)	102 (34%)
Headache	6 (3%)	9 (4%)	11 (4%)	16 (5%)
Back pain	2 (<1%)	1 (<1%)	2 (<1%)	5 (2%)
Abdominal pain	0 (0%)	1 (<1%)	6 (2%)	3 (1%)
Nausea	5 (2%)	5 (2%)	19 (6%)	18 (6%)
Constipation	2 (<1%)	6 (3%)	3 (1%)	3 (1%)
Vomiting	2 (<1%)	6 (3%)	12 (4%)	2 (<1%)
Diarrhea	4 (2%)	3 (1%)	11 (4%)	8 (3%)
Dyspepsia	2 (<1%)	4 (2%)	7 (2%)	2 (<1%)
LFTs abnormal	1 (<1%)	4 (2%)	1 (<1%)	3 (1%)
Dizziness	6 (3%)	4 (2%)	10 (3%)	6 (2%)
Hematuria	5 (2%)	2 (<1%)	0 (0%)	1 (<1%)
Urogenital surgery	4 (2%)	1 (<1%)	0 (0%)	0 (0%)
Vaginal moniliasis	0 (0%)	0 (0%)	10 (3%)	8 (3%)

Reviewer's Comment: The differences seen in adverse events between male and female patients treated with Cipro XR are not considered clinically meaningful and do not warrant reporting by sex in product labeling.

C. Race

Adverse events occurring in at least 2% of patients in any treatment group by race (Caucasian, Hispanic, Black) is shown in Table 61. Conclusions cannot be made for patients categorized as Asian or American Indian because their numbers are too small for a meaningful comparison.

Adverse event rates generally are consistent across subgroups. The number of patients with any adverse event is comparable between the two treatments for Caucasian: 31% (129/410) for Cipro XR and 33% (138/414) for Cipro BID and Hispanic 27% (13/48) for Cipro XR and 30% (16/53) for Cipro BID patients. Black patients treated with Cipro XR have a higher incidence of adverse events [38% (21/55)] compared with Black patients treated with Cipro BID [23% (11/48)]. This is due primarily to adverse events attributed to the urogenital system: 16% (9/55) in Cipro XR-treated patients versus 8% (4/48) Cipro BID-treated patients.

Within the Cipro XR group, more Hispanic patients developed nausea, headache, or vomiting than did black or Caucasian patients. In the Cipro BID group, Hispanic patients have a higher incidence of abdominal pain than did patients of the other two racial groups. There are no other notable differences between the two treatment groups by race. Overall, there are no clinically

meaningful differences in the incidence of adverse events across the three racial sub-groups (i.e., Caucasian, Black, and Hispanic).

TABLE 61
Incidence Rates of Adverse Events by Race
Occurring in at least 2% of Patients of Any Race by Treatment Group
Patients Valid for Safety

Adverse Event	n (%)					
	Caucasian		Hispanic		Black	
	Cipro XR N = 410	Cipro BID N = 414	Cipro XR N = 48	Cipro BID N = 53	Cipro XR N = 55	Cipro BID N = 48
Any Body System						
Any Event	129 (31)	138 (33)	13 (27)	16 (30)	21 (38)	11 (23)
Body As A Whole						
Any Event	42 (10)	47 (11)	7 (15)	7 (13)	5 (9)	4 (8)
Headache	12 (3)	20 (5)	4 (8)	3 (6)	1 (2)	2 (4)
Abdominal Pain	5 (1)	1 (<1)	1 (2)	3 (6)	0 (0)	0 (0)
Back Pain	0 (0)	5 (1)	0 (0)	0 (0)	0 (0)	1 (2)
Asthenia	0 (0)	2 (<1)	0 (0)	1 (2)	0 (0)	0 (0)
Sepsis	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Chest pain	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)
Digestive System						
Any Event	58 (14)	59 (14)	8 (17)	5 (9)	5 (9)	3 (6)
Nausea	18 (4)	21 (5)	6 (13)	1 (2)	0 (0)	1 (2)
Diarrhea	14 (3)	8 (2)	0 (0)	1 (2)	1 (2)	2 (4)
Vomiting	8 (2)	6 (1)	4 (8)	1 (2)	2 (4)	1 (2)
Dyspepsia	8 (2)	5 (1)	1 (2)	0 (0)	0 (0)	1 (2)
Constipation	0 (0)	8 (2)	0 (0)	1 (2)	0 (0)	0 (0)
LFTs abnormal	0 (0)	6 (1)	0 (0)	1 (2)	0 (0)	0 (0)
Anorexia	0 (0)	3 (<1)	1 (2)	0 (0)	1 (2)	1 (2)
Heme and Lymphatic System						
Any Event	4 (<1)	3 (<1)	0 (0)	0 (0)	1 (2)	1 (2)
Anemia	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Metabolic and Nutritional System						
Any Event	7 (2)	2 (<1)	1 (2)	1 (2)	0 (0)	0 (0)
Dehydration	4 (<1)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Musculoskeletal System						
Any Event	5 (1)	10 (2)	0 (0)	2 (4)	1 (2)	0 (0)
Arthralgia	2 (<1)	2 (<1)	0 (0)	2 (4)	1 (2)	0 (0)
Myalgia	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Nervous System						
Insomnia	0 (0)	2 (<1)	0 (0)	1 (2)	0 (0)	0 (0)
Hypertonia	2 (<1)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Respiratory System						
Any Event	16 (4)	18 (4)	1 (2)	1 (2)	2 (4)	2 (4)
Pharyngitis	4 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)

Adverse Event	n (%)					
	Caucasian		Hispanic		Black	
	Cipro XR N = 410	Cipro BID N = 414	Cipro XR N = 48	Cipro BID N = 53	Cipro XR N = 55	Cipro BID N = 48
Rhinitis	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Dyspnea	2 (<1)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Cough increased	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)
Skin and Appendages						
Any Event	7 (2)	7 (2)	1 (2)	1 (2)	1 (2)	2 (4)
Pruritus	0 (0)	2 (<1)	0 (0)	1 (2)	0 (0)	1 (2)
Special Senses						
Any Event	5 (1)	3 (<1)	1 (2)	1 (2)	1 (2)	1 (2)
Special senses surgery	2 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Urogenital System						
Any Event	26 (6)	28 (7)	4 (8)	2 (4)	9 (16)	4 (8)
Vaginal Moniliasis	7 (2)	8 (2)	2 (4)	0 (0)	1 (2)	0 (0)
Hematuria	4 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Dysuria	2 (<1)	3 (<1)	0 (0)	1 (2)	1 (2)	0 (0)
Urinary retention	4 (<1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Vaginitis	1 (<1)	0 (0)	1 (2)	1 (2)	1 (2)	2 (4)
Urogenital surgery	2 (<1)	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)

Note: Incidence rates = Number of events / Number of patients, where number of events is the number of patients reporting the event with a start date during or after treatment

Note: Asian and American Indian races are not shown because of small numbers.

Reviewer's Comment: The differences seen in adverse events between racial subgroups treated with Cipro XR are not considered clinically meaningful and do not warrant reporting by race in product labeling.

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XII. Clinical Reviewer's Conclusions of Study 100275

A. Efficacy Conclusions

Cipro XR was evaluated for the treatment of complicated urinary tract infections (cUTI) and acute uncomplicated pyelonephritis (AUP) in a randomized, double-blind, controlled clinical trial conducted in the US and Canada. The study enrolled 1,042 patients and compared Cipro XR (1000 mg once daily for 7 to 14 days) with immediate-release ciprofloxacin (500 mg twice daily for 7 to 14 days). The primary endpoint for this trial is bacteriologic eradication, of the baseline organism(s) with no new infection or superinfection, at 5 to 11 days post-therapy.

In the applicant's analysis, bacteriologic eradication in AUP and cUTI patients combined in the valid for efficacy (Per Protocol) population is 88.8% (183/206) in the Cipro XR group and 85.2% (85.2%) in the Cipro BID group. The 95% confidence interval using the Mantel-Haenszel estimate for the treatment difference in eradication rates (-2.4%, 10.3%) lies above -10%, indicating the non-inferiority of Cipro XR 1000 mg QD compared to Cipro 500 mg BID.

There are several problems with the applicant's analysis of bacteriologic eradication in cUTI and AUP patients combined in the Per Protocol (PP) population.

- First, there is a difference in the treatment effect between patients with AUP and cUTI. The eradication rates for the AUP patients are higher in the Cipro BID group (98.1%) than in the Cipro XR group (87.5%). In contrast the eradication rates for cUTI patients are higher in the Cipro XR group (89.2%) than in the ciprofloxacin BID group (81.4%). The *P* value from the Breslow-Day test for treatment-by-infection interaction is significant at 0.008, indicating that the treatment effect is different between AUP patients and cUTI patients. The Division does not consider it appropriate to pool efficacy results for cUTI and AUP patients due to the significant treatment-by-infection interaction.
- Second, although not specified by the applicant, the Division defined a Modified-to-Treat (MITT) population that includes all patients with a causative organism(s) isolated at baseline and who received at least one dose of study medication. When the MITT population is examined along with reasons for exclusion from the PP population, there are significantly more patients in the Cipro XR group (40%, 136/342) than in the Cipro BID group (29%, 95/324) that had been excluded from the PP population. Exclusions from the PP population are primarily a result of premature discontinuations, which are primarily due to adverse events (2.9% versus 1.7%, respectively) and no valid test-of-cure (TOC) urine culture or lost to follow-up (7.7% versus 4.6%, respectively). A differential rate in exclusion may bias the results of any analysis using this population.

Therefore, the bacteriologic eradication rates for AUP and cUTI were calculated separately by the FDA statistical reviewer and reported for both the MITT and PP populations. Since in the applicant's analysis random assignment of treatment was stratified by infection type, the calculation of the difference in eradication

rates between treatment groups for each stratum alone must be adjusted for multiple comparisons (i.e., 97.5% confidence intervals). The bacteriologic eradication rates and their corresponding 97.5% confidence intervals for the differences between rates (Cipro XR minus Cipro BID) for AUP and cUTI patients, at the TOC visit are given in the following table for both the MITT and PP populations.

**Bacteriologic Eradication at TOC (+5 to +11 Days)
in AUP and cUTI Patients**

	MITT*		PP**	
	n/N (% of Patients)	[95% CI of the Difference]	n/N (% of Patients)	[95% CI of the Difference]
AUP Patients				
Cipro XR	47/71 (66.2%)	[-26.8, 6.5]	35/40 (87.5%)	[-34.8, 6.2]
Cipro BID	58/76 (76.3%)		51/52 (98.1%)	
cUTI Patients				
Cipro XR	160/271 (59.0%)	[-13.5, 5.7]	148/166 (89.2%)	[-0.7, 16.3]
Cipro BID	156/248 (62.9%)		144/177 (81.4%)	

* Patients excluded from the Modified Intent-to-Treat group are those with no causative organism at baseline and those who did not receive study drug.

** Patients excluded from the Per Protocol group are those with no causative organism(s) at baseline, no valid TOC urine culture, inclusion/exclusion criteria violation, organism resistant to study drug, protocol violation, non-compliance with dosage regimen, did not receive study drug, inadequate duration of treatment, post-therapy antibiotics, and concomitant antimicrobial therapy.

For AUP patients, the 97.5% confidence interval for the treatment difference in bacteriologic eradication rates is below -10% in both the MITT and PP populations, indicating the conditions for non-inferiority of Cipro XR compared to Cipro BID were not met. For cUTI patients, the 97.5% confidence interval of difference is above -10% in the MITT and PP populations (and almost above zero in the PP population), indicating non-inferiority of Cipro XR compared to Cipro BID (and a trend toward superiority in one analysis).

Additional analyses were performed in an attempt to assess how Cipro XR compares to Cipro BID with respect to persistence of the baseline pathogen, and subsequent clinical response.

The applicant's definition in this study of bacteriologic eradication considers patients with new infections and superinfections to be treatment failures. In the PP population, of the 40 patients with AUP treated with Cipro XR, 35 were eradicated, 2 had persistence (1 *E. coli* and 1 *E. faecalis*), and 3 developed new infections with *E. faecalis* (2 with *E. coli* as baseline pathogen and one with *S. saprophyticus*). Of the 52 patients with AUP treated with Cipro BID, 51 were eradicated. One patient had persistence of *E. faecalis*.

The most common organism isolated from the urine of AUP patients is *E. coli*. The bacteriologic eradication rate for *E. coli* in the PP population is 97.2% (35/36) for the Cipro XR group and 100% (41/41) in the Cipro BID group.

In the PP population, of the 166 patients with cUTI treated with Cipro XR, 148 were eradicated, 8 had persistence, 5 patients developed superinfections, and 5 patients developed new infections. Of the 177 patients with cUTI treated with Cipro BID, 144 were eradicated, 16 had persistence, 3 patients developed superinfections, and 14 fourteen developed new infections.

The most common organisms isolated from the urine of cUTI patients are *E. coli*, *K. pneumoniae*, *E. faecalis*, and *P. mirabilis*. The bacteriologic eradication rates of these organisms in the PP population, in order, are 96.8% (91/94), 95.2% (20/21), 100% (17/17), and 91.6% (11/12) for the Cipro XR group. In the PP population of the Cipro BID group, the rates, in order, are 97.8% (90/92), 82.6% (19/23), 66.7% (14/21), and 100% (10/10).

Results for all the applicant's secondary variables (i.e., bacteriological response at the late follow-up visit and clinical response at the test-of-cure and late follow-up visits), in the PP population for AUP and cUTI patients separately, are summarized as follows:

- The bacteriologic eradication rates at the late follow-up visit in AUP patients are lower in the Cipro XR group (62.5%, 25/40) compared to the Cipro BID group (67.3%, 35/52). In cUTI patients, the rates are higher in the Cipro XR group (59.6%, 99/166) compared to the Cipro BID group (45.2%, 80/177). The differences between the two patient groups follows a similar trend to the results at the TOC visit.
- The clinical response at the TOC visit in AUP patients is similar for the Cipro XR and Cipro BID groups [97.5% (39/40) and 96.2% (50/52), respectively]. In cUTI patients, the response rates are slightly higher in the Cipro XR group (95.8%, 159/166) compared to the Cipro BID group (91.0%, 161/177).
- The clinical response at the late follow-up visit in AUP patients is slightly lower for the Cipro XR group (75%, 30/40) compared to Cipro BID group (80.8%, 42/52). In cUTI patients, the response rates are slightly higher in the Cipro XR group (72.3%, 120/166) compared to the Cipro BID group (61.6%, 109/177).

Differences seen, if any, in bacteriologic eradication rates between younger and older patients, males and females, and those of various races are not considered clinically meaningful and no adjustments to the dosing of Cipro XR are warranted based on age, sex, or race.

B. Safety Conclusions

Of the 1042 patients enrolled in the study, 1035 received at least one dose of study drug and are valid for the analysis of safety (517 in the Cipro XR group and 518 in the Cipro BID group). The proportion of patients who experienced at least one adverse event (31.9%) is the same in both treatment groups.

More patients in the Cipro XR group (28 patients or 5.4%) than in the Cipro BID group (19 patients or 3.7%) discontinued study drug due to an adverse event.

The most common reasons for discontinuation, regardless of attributability to study drug, in the Cipro XR group are dizziness and nausea/vomiting [both 25% (5/28)] and headache [11% (3/28)]. In the Cipro BID group the most common reasons for discontinuation are nausea/vomiting and LFT abnormalities [both 21% (4/19)] and diarrhea [11% (2/19)]. No patient discontinued due to dizziness in the Cipro BID group.

The most common adverse events in both treatment groups are those occurring in the digestive system [14% (71/517) for Cipro XR and 13% (67/518) for Cipro BID]. The incidence of adverse events for each body system is similar between treatment groups, except for the nervous system. Six percent (6%) of patients in the Cipro XR group (30/517) experienced at least one adverse event involving the nervous system compared with 4% (20/518) in the of Cipro BID group. The events primarily responsible for this difference are dizziness (16 patients [3%] in the Cipro XR group versus 10 patients [2%] in the Cipro BID group), and abnormal dreams, depression, hallucinations, stupor, thinking abnormal, tremor, and hypesthesia (1 patient for each [$<1\%$] versus 0 patients [0%], respectively).

Most patients in both treatment groups who experienced adverse events had events that were assessed by the investigator as mild or moderate in intensity. Adverse events that occurred in at least 2% of patients treated with Cipro XR include nausea (5%), headache (3%), diarrhea (3%), vomiting (3%), dizziness (3%), dyspepsia (2%), and vaginal moniliasis (2%). Cipro BID has a similar profile of adverse events occurring in at least 2% of patients, with a slightly higher incidence of headache (5%).

Study drug-related (possible or probable relationship) adverse events were reported in 13% (68/517) of patients in the Cipro XR group and 14% (70/518) of patients in the Cipro BID group. Those occurring in 2% or more of patients in either treatment group include headache, nausea, diarrhea, dizziness, and vaginal moniliasis.

A small proportion of patients had events that were assessed by the investigator as severe in intensity. Seven percent (35/517) of all valid for safety patients in the Cipro XR group and 5% (28/518) in the Cipro BID group experienced at least one adverse event assessed by the investigator as severe in intensity. The number of severe adverse events represents 14.6% (50/342) and 12.8% (39/304), respectively, of the total number of adverse events reported.

Four patient deaths were reported during the study (3 in the Cipro XR group and one in the Cipro BID group). All four patients were in the older age range (76 to 95 years), had a diagnosis of cUTI with one underlying condition, and had other concurrent medical conditions requiring concomitant medications. In all cases, the adverse event resulting in death was judged by the investigator to be of unlikely or no relationship to study drug and the FDA reviewer concurred.

Patients experiencing non-fatal serious adverse events (SAEs) is 5% in both treatment groups, (28/517 and 24/518, respectively). All SAEs reported in the Cipro XR group were judged by the investigators to be unlikely or not related to study drug.

In the two treatment groups, the incidence of clinically significant ($>1.8 \times$ ULN) abnormalities in SGOT and SGPT is the same (2%). For abnormalities in SGOT and SGPT that are $>3 \times$ ULN, the incidence is 1% in the Cipro XR group and 2% in the Cipro BID group. Two patients ($<1\%$) in the Cipro XR group had liver function test abnormalities that were reported as adverse events. In both cases, the events resolved and did not require discontinuation of study drug. Seven patients (1%) treated with Cipro BID had abnormal liver function test results that were reported as adverse events. In 4 of these 7 patients, the liver function test abnormalities were a reason for discontinuation of study medication. Only one of the 4 patients in the Cipro BID group who discontinued prematurely for liver function test abnormalities had all tests within the normal range at baseline.

The incidence of other laboratory test abnormalities is low and comparable between the two treatment groups. Descriptive statistics of the change from baseline in laboratory test results does not reveal any trends that appear to be uniquely associated with Cipro XR treatment.

Overall, there are no clinically meaningful differences in the safety profile of either treatment on the basis of age, sex, or race.

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APPENDIX 2 – ADDITIONAL TABLES FOR STUDY 100275

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Table 2 is modified from the applicant's submission by the reviewer for clarity

TABLE 2
List of Investigators and Number of Patients per Treatment Arm
All Randomized (N=1042)

Site Number	Principal Investigator	Treatment Arm					
		Ciprofloxacin XR (N=521)			Ciprofloxacin BID (N=521)		
		Randomized	Valid for Safety	Per Protocol	Randomized	Valid for Safety	Per Protocol
2	Bastuba	1	1	0	1	1	0
4	Bergreen	3	3	1	2	2	1
6	Childs	10	10	5	10	10	5
12	Durden	4	4	2	4	4	1
13	Elashker	4	4	1	3	3	2
15	Foote	9	9	3	10	10	4
16	Casey	0	0	0	1	1	1
17	Garcia	4	4	1	4	4	1
18	Giordano	6	6	2	5	5	2
19	Goldfischer	9	9	2	7	7	1
20	Hellstrom	7	7	2	6	6	1
25	Klimberg	10	10	5	17	17	12
26	Knapp	6	6	3	7	7	4
27	Auerbach	5	5	1	5	5	1
29	Mullins	8	8	1	6	6	3
31	McMurray	10	10	7	11	11	4
34	Raad	0	0	0	1	1	1
35	Rafelson	0	0	0	1	1	1
36	Randall	8	6	2	9	8	4
37	Rosenberg	3	3	1	3	3	1
38	Rozas	1	1	0	1	1	0
39	Saltzstein	3	3	2	3	3	2
40	Shami	4	4	1	3	3	2
41	Sharifi	8	8	4	9	9	8
42	Siami	27	27	11	30	30	16
45	Taub	19	19	7	19	19	10
48	Wegenke	16	16	10	16	16	9
49	Young	24	24	12	23	23	9
50	Zinner	6	6	3	6	6	5
51	Fiel	1	1	1	0	0	0
52	Colan	7	7	1	6	6	1
53	Brown	15	15	7	16	16	8
54	Elliott	1	1	0	0	0	0
59	Feldman	16	16	5	16	16	4
62	McCarron	10	10	4	8	7	5
63	Mirelman	8	8	2	7	7	5
64	Moseley	7	7	4	5	5	1
66	Ott	0	0	0	1	1	0

Site Number	Principal Investigator	Treatment Arm					
		Ciprofloxacin XR (N=521)			Ciprofloxacin BID (N=521)		
		Randomized	Valid for Safety	Per Protocol	Randomized	Valid for Safety	Per Protocol
68	Schiff	6	6	1	4	4	1
70	Snyder	2	2	0	1	1	0
73	Tomera	20	20	7	22	21	7
74	Wells	8	8	2	7	7	4
75	Shockey	3	3	1	3	3	2
76	Dahdul	5	5	2	6	6	2
77	Kaminetsky	5	5	2	5	5	3
82	Talan	12	12	5	15	15	7
86	Canfield	3	3	0	2	2	2
88	Panebianco	1	1	0	1	1	0
89	Teitelbaum	0	0	0	1	1	0
90	Wolf-Klein	1	1	1	2	2	1
91	Hoffman	3	3	1	3	3	1
92	Stringer	7	7	5	6	6	4
94	Fawzy	1	1	0	0	0	0
95	Wachs	19	18	4	20	20	7
97	Beckett	2	2	0	1	1	1
98	Elist	1	1	1	0	0	0
100	Daboul	1	1	0	2	2	0
101	Freeman	3	3	1	4	4	2
102	Misurec	11	11	7	11	11	5
105	Kim	1	1	1	3	3	3
106	Freeman	3	3	2	3	3	2
109	Chu	3	3	0	4	4	2
110	Patsias	2	2	0	0	0	0
111	Rigby	1	1	1	0	0	0
115	Saslowsky	0	0	0	1	1	1
116	Wall	1	1	0	0	0	0
118	Gin-Shaw	8	7	2	8	8	1
119	Whitlock	2	2	0	3	3	1
120	Parramore	3	3	2	3	3	1
123	Castellano	3	3	0	3	3	2
124	Maggiacomo	3	3	0	2	2	0
125	Peters-Gee	4	4	3	2	2	0
127	Stallings	2	2	1	2	2	2
129	Ackerman	1	1	0	2	2	1
130	Nafziger	1	1	0	0	0	0
132	Kotkin	0	0	0	1	1	1
133	Vacker	2	2	0	2	2	1
137	George	2	2	0	2	2	1
138	Bowman	3	3	2	2	2	0
139	Nevins	2	2	2	2	2	1
141	Duffin	1	1	1	0	0	0
142	Efros	8	8	5	6	6	3

Site Number	Principal Investigator	Treatment Arm					
		Ciprofloxacin XR (N=521)			Ciprofloxacin BID (N=521)		
		Randomized	Valid for Safety	Per Protocol	Randomized	Valid for Safety	Per Protocol
145	Marks	0	0	0	1	1	0
148	Oberoi	14	14	3	14	14	5
149	Gezon	2	2	0	4	4	2
150	Swierzewski	2	2	1	1	1	0
151	Brownstone	5	5	3	5	5	1
153	Howard	0	0	0	1	1	0
155	Frankel	1	1	0	0	0	0
157	Phillips	1	1	0	1	1	1
159	Leff	0	0	0	1	1	0
160	Schneiderman	1	1	0	2	2	0
201	Casey	3	3	2	2	2	1
202	Valiquette	0	0	0	2	2	0
205	Shu	8	8	5	5	5	1
207	Nicolle	4	4	2	4	4	1
208	Nickel	2	2	1	0	0	0
209	O'Mahony	20	20	12	22	22	10
211	Barkin	5	5	1	4	4	0
213	Kuzmarov	3	3	1	3	3	0
TOTAL		521	517	206	521	518	229

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TABLE 14
Bacteriological Eradication Rates at Test-of-Cure Visit (+5 to +11 days)
Patients Valid for Efficacy

Organism	Cipro XR			Cipro BID		
	Erad (%)	Pers (%)	Indeter (%)	Erad (%)	Pers (%)	Indeter (%)
Urine						
AUP Patients						
<i>Escherichia coli</i>	35 (97%)	1 (3%)	0	41 (100%)	0	0
cUTI Patients						
<i>Escherichia coli</i>	91 (97%)	3 (3%)	0	90 (98%)	2 (2%)	0
<i>Klebsiella pneumoniae</i>	20 (87%)	1 (4%)	2 (9%)	19 (83%)	4 (17%)	0
<i>Enterococcus faecalis</i>	17 (94%)	0	1 (6%)	14 (67%)	7 (33%)	0
<i>Proteus mirabilis</i>	11 (92%)	1 (8%)	0	10 (91%)	0	1 (9%)
<i>Enterobacter aerogenes</i>	4 (100%)	0	0	6 (100%)	0	0
<i>Pseudomonas aeruginosa</i>	3 (100%)	0	0	3 (100%)	0	0
Blood						
AUP Patients						
<i>Escherichia coli</i>	4 (80%)	0	1 (20%)	3 (75%)	0	1 (25%)
<i>Klebsiella pneumoniae</i>	1 (100%)	0	0	0	0	0
cUTI Patients						
<i>Escherichia coli</i>	1 (100%)	0	0	1 (100%)	0	0

Erad = eradication; Pers = persistence; Indeter = Indeterminate

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Reviewer's Comment: Tables 15 through 19 are from the microbiologist's review.

TABLE 15
Microbiological Response by MIC for AUP Patients
Patients Valid for Efficacy

Organism	MIC (µg/mL)	Outcome	Cipro XR		Cipro BID	
			Number	%	Number	%
AUP Patients—Urine						
<i>Escherichia coli</i>	0.008	Eradication	1	100	3	100
	0.015	Eradication	24	96	25	100
		Persistence	1	4	0	0
	0.03	Eradication	6	100	7	100
	0.06	Eradication	2	100	2	100
	0.12	Eradication	1	100	1	100
	0.25	Eradication	0	0	1	100
	0.5	Eradication	1	100	2	100
	ALL	Eradication	35	97	41	100
		Persistence	1	3	0	0
AUP Patients--Blood						
<i>Escherichia coli</i>	0.015	Eradication	4	80	0	0
		Indeterminate	1	20	1	100
	0.03	Eradication	0	0	1	100
	0.12	Eradication	0	0	1	100
	0.25	Eradication	0	0	1	100
	ALL	Eradication	4	80	3	75
		Indeterminate	1	20	1	25
<i>Klebsiella pneumoniae</i>	0.03	Eradication	1	100	0	0
	ALL	Eradication	1	100	0	0

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TABLE 16
Microbiological Responses by MIC for cUTI Patients
Patients Valid for Efficacy

Organism	MIC (µg/mL)	Outcome	Cipro XR		Cipro BID		
			Number	%	Number	%	
cUTI Patients—Urine							
<i>Escherichia coli</i>	0.008	Eradication	10	100	6	100	
	0.015	Eradication	54	98	50	98	
		Persistence	1	2	1	2	
	0.03	Eradication	19	100	24	100	
	0.06	Eradication	4	80	3	100	
		Persistence	1	20	0	0	
	0.12	Eradication	0	0	5	100	
		Eradication	2	100	1	50	
	0.25	Persistence	0	0	1	50	
		Eradication	2	67	0	0	
	0.5	Persistence	1	33	0	0	
		Eradication	0	0	1	100	
	ALL	Eradication	91	97	90	98	
		Persistence	3	3	2	2	
	<i>Enterococcus faecalis</i>	0.25	Eradication	0	0	1	50
			Persistence	0	0	1	50
		0.5	Eradication	6	100	3	50
			Persistence	0	0	3	50
1		Eradication	11	100	8	89	
		Persistence	0	0	1	11	
2		Eradication	0	0	2	50	
		Persistence	0	0	2	50	
ALL		Indeterminate	1	100	0	0	
		Eradication	17	94	14	67	
		Persistence	0	0	7	33	
<i>Klebsiella pneumoniae</i>		0.015	Indeterminate	1	6	0	0
	Eradication		1	100	1	100	
	Eradication		4	67	10	83	
	0.03	Persistence	0	0	2	17	
		Indeterminate	2	33	0	0	
	0.06	Eradication	5	83	4	67	
		Persistence	1	17	2	33	
	0.12	Eradication	2	100	1	100	
	0.25	Eradication	4	100	0	0	
	0.5	Eradication	2	100	2	100	
1.0	Eradication	2	100	1	100		
ALL	Eradication	20	87	19	83		
	Persistence	1	4	4	17		
	Indeterminate	2	9	0	0		
<i>Proteus mirabilis</i>	0.015	Eradication	2	100	0	0	
	0.03	Eradication	5	100	5	100	
		Eradication	3	75	1	100	
	0.06	Persistence	1	25	0	0	
		Eradication	0	0	1	100	
	0.12	Indeterminate	0	0	1	100	
0.5	Indeterminate	0	0	1	100		
1	Eradication	1	100	0	0		

Organism	MIC (µg/mL)	Outcome	Cipro XR		Cipro BID	
			Number	%	Number	%
	2	Eradication	0	0	3	100
	ALL	Eradication	11	92	10	91
		Persistence	1	8	0	0
		Indeterminate	0	0	1	9
<i>Enterobacter aerogenes</i>	0.015	Eradication	1	100	1	100
	0.03	Eradication	1	100	4	100
	0.06	Eradication	2	100	0	0
	0.25	Eradication	0	0	1	100
	ALL	Eradication	4	100	6	100
<i>Pseudomonas</i>	0.12	Eradication	2	100	2	100
<i>aeruginosa</i>	0.25	Eradication	0	0	1	100
	0.5	Eradication	1	100	0	0
	ALL	Eradication	3	100	3	100
cUTI Patients—Blood						
<i>Escherichia coli</i>	0.015	Eradication	1	100	0	0
	0.12	Eradication	0	0	1	100
	ALL	Eradication	1	100	1	100

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Reviewer's Comment: Tables 17 and 18 were modified from the microbiologist's review by the reviewer for clarity.

TABLE 17
Patients with Bacteriologic Persistence or Clinical Failure
Cipro XR Group
Patients Valid for Efficacy

Patient #	Organism	Cipro MIC	Bact Resp At TOC	Bact Resp At FU	Clin Resp At TOC	Clin Resp At FU
15005	<i>E. coli</i>	0.06	Persistence	Persistence	Cure	
31006	<i>P. mirabilis</i>	0.06	Persistence	Persistence	Cure	Relapse
31012	<i>E. faecalis</i>	1.0	Eradication	Indeterminate	Failure	Failure
42012	<i>S. aureus</i>	2.0	Persistence	Persistence	Cure	
42056	<i>C. freundii</i>	0.12	Persistence	Persistence	Failure	Failure
48037	<i>S. aureus</i>	0.25	Persistence	Persistence	Cure	
49061	<i>E. coli</i>	0.5	Persistence	Persistence	Cure	Con. Cure
73042	<i>K. pneumoniae</i>	0.25	Eradication	Indeterminate	Failure	Failure
77018	<i>E. coli</i>	0.015	Persistence	Persistence	Relapse	Relapse
98001	<i>K. pneumoniae</i>	0.06	Persistence	Persistence	Cure	Failure
125006	<i>K. pneumoniae</i>	0.25	Eradication	Indeterminate	Failure	Failure
127001	<i>E. faecalis</i>	2.0	Indeterminate	Indeterminate	Failure	Failure
127001	<i>K. pneumoniae</i>	0.03	Indeterminate	Indeterminate	Failure	Failure
209029	<i>E. coli</i>	0.015	Persistence	Persistence	Cure	Relapse
209039	<i>E. faecalis</i>	1.0	Persistence	Persistence	Failure	Failure

Cipro = ciprofloxacin; Bact Resp = bacteriological response; Clin Resp = clinical response

TOC = test-of-cure; FU = follow-up

Con. Cure = continued cure; Con. Erad. = continued eradication

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TABLE 18
Patients with Bacteriologic Persistence or Clinical Failure
Cipro BID Group
Patients Valid for Efficacy

Patient #	Organism	Cipro MIC	Bact Resp At TOC	Bact Resp At FU	Clin Resp At TOC	Clin Resp At FU
12002	<i>E. coli</i>	0.015	Eradication	Indeterminate	Failure	Failure
13017	<i>E. faecalis</i>	1.0	Persistence	Persistence	Cure	Con. Cure
15011	<i>K. pneumoniae</i>	0.03	Persistence	Persistence	Cure	Relapse
25005	<i>K. oxytoca</i>	0.5	Persistence	Persistence	Cure	Relapse
25029	<i>E. faecalis</i>	1.0	Persistence	Persistence	Cure	Con. Cure
25029	<i>E. coli</i>	0.03	Eradication	Con. Erad	Cure	Con. Cure
42038	<i>C. koseri</i>	0.5	Persistence	Persistence	Cure	Failure
45019	<i>E. faecalis</i>	0.5	Persistence	Persistence		
48013	<i>E. coli</i>	0.03	Eradication	Indeterminate	Failure	Failure
53029	<i>K. pneumoniae</i>	0.06	Eradication	Persistence	Failure	Failure
59033	<i>K. pneumoniae</i>	0.5	Eradication	Indeterminate	Failure	Failure
73046	<i>E. faecalis</i>	0.25	Persistence	Persistence	Cure	Con. Cure
73046	<i>E. coli</i>	0.015	Eradication	Con. Erad	Cure	Con. Cure
74015	<i>K. pneumoniae</i>	0.03	Persistence	Persistence	Failure	Failure
76011	<i>K. pneumoniae</i>	0.06	Persistence	Persistence	Failure	Failure
77006	<i>E. coli</i>	0.015	Persistence	Persistence		
91008	<i>E. coli</i>	0.25	Persistence	Persistence	Failure	Failure
92011	<i>E. faecalis</i>	1.0	Eradication	Indeterminate	Failure	Failure
92011	<i>S. marcescens</i>	1.0	Eradication	Indeterminate	Failure	Failure
97001	<i>S. aureus</i>	0.5	Persistence	Persistence	Relapse	Relapse
101007	<i>E. faecalis</i>	2.0	Persistence	Persistence	Cure	
106019	<i>K. pneumoniae</i>	0.03	Eradication	Indeterminate	Failure	Failure
127006	<i>E. faecalis</i>	0.5	Persistence	Persistence	Failure	Failure
129001	<i>E. faecalis</i>	2.0	Persistence	Persistence	Failure	Failure
133008	<i>E. coli</i>	0.03	Eradication	Indeterminate	Failure	Failure
201006	<i>E. faecalis</i>	0.5	Persistence	Persistence	Failure	Failure

Cipro = ciprofloxacin; Bact Resp = bacteriological response; Clin Resp = clinical response
 TOC = test-of-cure; FU = follow-up
 Con. Cure = continued cure; Con. Erad. = continued eradication

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TABLE 19
Organisms with Elevated MICs Post-Therapy^a

Organism	MIC (µg/mL)		Eradication	
	Pre-Therapy	Post-Therapy	TOC	FU
<i>Escherichia coli</i>				
Cipro XR group	0.015	0.12	No	No
	0.03	0.5	Yes	Recurred
	0.03	16	Yes	Recurred
	0.06	16	Yes	Recurred
Cipro BID group	0.015	0.5	Yes	Recurred
	0.015	1.0	Yes	Recurred
	0.015	16	No	No
<i>Enterococcus faecalis</i>				
Cipro BID group	0.5	2	No	No
	1	16	No	No
<i>Klebsiella pneumoniae</i>				
Cipro XR group	0.06	0.5	No	No
<i>Staphylococcus aureus</i>				
Cipro XR group	2	16	No	No

^a MIC at post-therapy greater than one dilution higher than MIC at pre-therapy

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TABLE 40
Number of Patients (%) with Bacteriological Response
at the TOC Visit (+5 to +11 Days)
Patients Valid for Safety

	Cipro XR	Cipro BID
<i>All Patients</i>	(N=327)	(N=315)
Eradication	207 (63.3%)	214 (67.9%)
Persistence	24 (7.3%)	33 (10.5)
Superinfection	5 (1.5%)	3 (1.0%)
New infection	9 (2.8%)	16 (5.1%)
Indeterminate	82 (25.1%)	49 (15.6%)
Eradication Rate^a	207/327 (63.3%)	214/327 (67.9%)
<i>AUP Patients</i>	(N=71)	(N=76)
Eradication	47 (66.2%)	58 (76.3%)
Persistence	3 (4.2%)	3 (3.9%)
New infection	3 (4.2%)	1 (1.3%)
Indeterminate	18 (25.4%)	14 (18.4%)
<i>cUTI Patients</i>	(N=256)	(N=239)
Eradication	160 (62.5%)	156 (65.3%)
Persistence	21 (8.2%)	30 (12.6%)
Superinfection	5 (2.0%)	3 (1.0%)
New infection	6 (2.3%)	15 (6.3%)
Indeterminate	64 (25.0%)	35 (14.6%)

^a Eradication rate for all patients (cUTI plus AUP), including indeterminate responses; Estimate of the difference in rates -4.4% [Mantel-Haenszel 95% CI (-11.8%, 2.9%)]

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TABLE 41
Number of Patients (%) with Bacteriological Response at the
Follow-up Visit (+28 to +42 Days)
Patients Valid for Safety

	Cipro XR	Cipro BID
<i>All Patients</i>	(N=327)	(N=315)
Continued eradication	146 (44.6%)	130 (41.3%)
Eradication w/recurrence	22 (6.7%)	24 (7.6%)
Persistence	24 (7.3%)	31 (9.8%)
Superinfection	5 (1.5%)	2 (0.6%)
New infection	30 (9.2%)	42 (13.3%)
Indeterminate	100 (30.6%)	86 (27.3%)
Eradication Rate^a	146/327 (44.6%)	130/315 (41.3%)
<i>AUP Patients</i>	(N=71)	(N=76)
Continued eradication	35 (49.3)	41 (53.9%)
Eradication w/recurrence	1 (1.4%)	4 (5.3%)
Persistence	3 (4.2%)	3 (3.9%)
New infection	5 (7.0%)	5 (6.6%)
Indeterminate	27 (38.0%)	23 (30.3%)
Continued Eradication Rate^b	35/71 (49.3)	41/76 (53.9%)
<i>cUTI Patients</i>	(N=256)	(N=239)
Continued eradication	111 (43.4%)	89 (37.2%)
Eradication w/recurrence	21 (8.2%)	20 (8.4%)
Persistence	21 (8.2%)	28 (11.7%)
Superinfection	5 (2.0%)	2 (0.8%)
New infection	25 (9.8%)	37 (15.5%)
Indeterminate	73 (28.5%)	63 (26.4%)
Continued Eradication Rate^c	111/256 (43.4%)	89/239 (37.2%)

^a Eradication rate for all patients (cUTI plus AUP); the follow-up rates in this population include the indeterminate responses. Estimate of the difference in rates 3.6% [Mantel-Haenszel 95% CI (-4.0%, 11.3%)]

^b Continued eradication rate for AUP patients, including indeterminate responses.

^c Continued eradication rate for cUTI patients, including indeterminate responses.

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TABLE 42
Number of Patients (%) with Clinical Response at the TOC Visit (+5 to +11 Days)
Patients Valid for Safety

	Cipro XR	Cipro BID
<i>All Patients</i>	(N=517)	(N=518)
Cure	343 (66.3%)	366 (70.7%)
Continued cure	0 (0%)	1 (0.2%)
Improvement	0 (0%)	1 (0.2%)
Failure	35 (6.8%)	38 (7.3%)
Relapse	1 (0.2%)	1 (0.2%)
Indeterminate	11 (2.1%)	8 (1.5%)
Missing	127 (24.6%)	103 (19.9%)
Success Rate^a	343/517 (66.3%)	367/518 (70.8%)
<i>AUP Patients</i>	(N=109)	(N=111)
Cure	76 (69.7%)	85 (76.6%)
Continued cure	0 (0%)	1 (0.9%)
Improvement	0 (0%)	1 (0.9%)
Failure	6 (5.5%)	4 (3.6%)
Indeterminate	2 (1.8%)	1 (0.9%)
Missing	25 (22.9%)	19 (17.1%)
<i>cUTI Patients</i>	(N=408)	(N=407)
Cure	267 (65.4%)	281 (69.0%)
Failure	29 (7.1%)	34 (8.4%)
Relapse	1 (0.2%)	1 (0.2%)
Indeterminate	9 (2.2%)	7 (1.7%)
Missing	102 (25.0%)	84 (20.6%)

^a Success rate (cure plus continued cure) for all patients (cUTI plus AUP), including indeterminate or missing responses; Estimate of the difference in rates – 4.5%; [Mantel-Haenszel 95% CI (-10.1%, 1.2%)]

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TABLE 43
Number of Patients (%) with Clinical Response at the
Follow-up Visit (+28 to +42 Days)
Patients Valid for Safety

	Cipro XR	Cipro BID
<i>All Patients</i>	(N=517)	(N=518)
Cure	1 (0.2%)	1 (0.2%)
Continued cure	257 (49.7%)	269 (51.9%)
Failure	41 (7.9%)	43 (8.3%)
Relapse	33 (6.4%)	34 (6.6%)
Indeterminate	3 (0.6%)	7 (1.4%)
Missing	182 (35.2%)	164 (31.7%)
Success Rate^a	258/517 (49.9%)	270/518 (52.1%)
<i>AUP Patients</i>	(N=109)	(N=111)
Cure	1 (0.9%)	0 (0%)
Continued cure	59 (54.1%)	68 (61.3%)
Failure	6 (5.5%)	4 (3.6%)
Relapse	8 (7.3%)	0 (0%)
Missing	35 (32.1%)	39 (35.1%)
Success Rate^b	60/109 (55.0%)	68/111 (61.3%)
<i>cUTI Patients</i>	(N=408)	(N=407)
Cure	0 (0%)	1 (0.2%)
Continued cure	198 (48.5%)	201 (49.4%)
Failure	35 (8.6%)	39 (9.6%)
Relapse	25 (6.1%)	34 (8.4%)
Indeterminate	3 (0.7%)	7 (1.7%)
Missing	147 (36.0%)	125 (30.7%)
Success Rate^c	198/408 (48.5%)	201/407 (49.4%)

^a Success rate (cure plus continued cure) for all patients (cUTI plus AUP), including missing or indeterminate responses; Estimate of difference in rates -2.2% [Mantel-Haenszel 95% CI (-8.27%, 3.9%)]

^b Success rate (cure plus continued cure) for pyelonephritis patients, including missing or indeterminate responses.

^c Success rate (cure plus continued cure) for complicated UTI patients, including missing or indeterminate responses.

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Tables 47A, 47B, 48A and 48B were created by the reviewer.

TABLE 47A
Summary of Adverse Events
Patients Valid for Safety with Normal Renal Function CLcr > 80 mL/min

	Cipro XR (N=321)	Ciprofloxacin BID (N=323)
Any adverse event	88 (27.4%)	65 (20.1%)
Any drug-related adverse event*	34 (10.6%)	29 (9.0%)
Any serious adverse event	25 (7.8%)	15 (4.6%)

* possible, probable, and likely

TABLE 47B
Summary of Adverse Events
Patients Valid for Safety with Moderate Renal Impairment
CLcr = 30 to 50 mL/min

	Cipro XR (N=106)	Ciprofloxacin BID (N=96)
Any adverse event	33 (31.1%)	29 (30.2%)
Any drug-related adverse event*	13 (12.3%)	11 (11.5%)
Any serious adverse event	4 (3.8%)	5 (5.2%)

* possible, probable, and likely

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TABLE 48A
Incidence Rates of Adverse Events Occurring in at Least 2 Patients
by Treatment Group
Patients Valid for Safety with a Creatinine Clearance between 30 to 50 mL/min

Cipro XR (N=106)	n	%		Cipro BID (N=97)	n	%
NAUSEA	7	6.6		NAUSEA	8	8.2
DIARRHEA	5	4.7		DYSPEPSIA	4	4.1
DIZZINESS	4	3.8		PRURITUS	3	3.1
ASTHENIA	2	1.9		VOMITING	3	3.1
COLITIS	2	1.9		ACCIDENTAL INJURY	2	2.1
DEHYDRATION	2	1.9		ANOREXIA	2	2.1
FEVER	2	1.9		CORONARY ARTERY DISORDER	2	2.1
HEADACHE	2	1.9		DIARRHEA	2	2.1
HEMATURIA	2	1.9		DIZZINESS	2	2.1
HYPERTENSION	2	1.9		HEADACHE	2	2.1
MALaise	2	1.9		HEMORRHAGE	2	2.1
PERIPHERAL EDEMA	2	1.9		LIVER FUNCTION TESTS ABNORMAL	2	2.1
PNEUMONIA	2	1.9		PERIPHERAL EDEMA	2	2.1
SEPSIS	2	1.9				
UROGENITAL SURGERY	2	1.9				
VAGINAL MONILIASIS	2	1.9				
VOMITING	2	1.9				

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TABLE 48B
Incidence Rates of Adverse Events Occurring in at Least 2 Patients
by Treatment Group
Patients Valid for Safety with a Creatinine Clearance above 80 mL/min

Cipro XR (N=322)	n	%		Cipro BID (N=324)	n	%
HEADACHE	14	4.3		HEADACHE	19	5.9
NAUSEA	12	3.7		NAUSEA	11	3.4
DIARRHEA	9	2.8		DIARRHEA	7	2.2
VOMITING	9	2.8		DIZZINESS	7	2.2
VAGINAL MONILIASIS	7	2.2		LIVER FUNCTION TESTS ABNORMAL	7	2.2
DIZZINESS	6	1.9		VAGINAL MONILIASIS	7	2.2
DYSPEPSIA	6	1.9		CONSTIPATION	5	1.5
ABDOMINAL PAIN	3	0.9		ABDOMINAL PAIN	4	1.2
ARTHRALGIA	3	0.9		ACCIDENTAL INJURY	4	1.2
BACK PAIN	3	0.9		ARTHRALGIA	4	1.2
FLATULENCE	3	0.9		BACK PAIN	4	1.2
PHARYNGITIS	3	0.9		SINUSITIS	4	1.2
RHINITIS	3	0.9		FEVER	3	0.9
URINARY RETENTION	3	0.9		INSOMNIA	3	0.9
VAGINITIS	3	0.9		VAGINITIS	3	0.9
ANOREXIA	2	0.6		VOMITING	3	0.9
ASTHENIA	2	0.6		ANOREXIA	2	0.6
CONSTIPATION	2	0.6		ANXIETY	2	0.6
CYST	2	0.6		ARTHRITIS	2	0.6
DEHYDRATION	2	0.6		ASTHENIA	2	0.6
DYSURIA	2	0.6		COUGH INCREASED	2	0.6
FLU SYNDROME	2	0.6		DYSURIA	2	0.6
HYPERTONIA	2	0.6		FLATULENCE	2	0.6
INFECTION BACTERIAL	2	0.6		GI NEOPLASIA	2	0.6
INSOMNIA	2	0.6		LEG PAIN	2	0.6
KIDNEY CALCULUS	2	0.6		LUNG DISORDER	2	0.6
LIVER FUNCTION TESTS ABNORMAL	2	0.6		MYASTHENIA	2	0.6
MYALGIA	2	0.6		ORAL MONILIASIS	2	0.6
PELVIC PAIN	2	0.6		RECTAL HEMORRHAGE	2	0.6
PERIPHERAL EDEMA	2	0.6		RHINITIS	2	0.6
RASH	2	0.6		SEPSIS	2	0.6
SPECIAL SENSES SURGERY	2	0.6				

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/s/

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